Schizophrenia Research 210 (2019) 255–261

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

The influence of religious activity and polygenic schizophrenia risk on religious delusions in schizophrenia

Heike Anderson-Schmidt [a,b,*,1], Katrin Gade [a,b,1], Dörthe Malzahn [c,1,2], Sergi Papiol [a,d], Monika Budde [a], Urs Heilbronner [a], Daniela Reich-Erkelenz [a], Kristina Adorjan [a,d], Janos L. Kalman [a,d,e], Fanny Senner [a,d], Ashley L. Comes [a,e], Laura Flatau [a], Anna Gryaznova [a], Maria Hake [a], Markus Reitt [b], Max Schmauß [f], Georg Juckel [g], Jens Reimer [h], Jörg Zimmermann [h,i], Christian Figge [i], Eva Reininghaus [j], Ion-George Anghelescu [k], Carsten Konrad [l], Andreas Thiel [l], Martin von Hagen [m], Manfred Koller [n], Sebastian Stierl [o], Harald Scherk [p], Carsten Spitzer [q], Here Folkerts [r], Thomas Becker [s], Detlef E. Dietrich [t,u,3], Till F.M. Andlauer [v], Franziska Degenhardt [w,x], Markus M. Nöthen [w,x], Stephanie H. Witt [y], Marcella Rietschel [y], Jens Wiltfang [b,z,aa], Peter Falkai [d], Thomas G. Schulze [a,b]

[a] Institute of Psychiatric Phenomics and Genomics (IPPG), University Hospital, LMU Munich, Munich 80336, Germany
[b] Department of Psychiatry and Psychotherapy, University Medical Center Göttingen, Göttingen 37075, Germany
[c] Department of Genetic Epidemiology, University Medical Center Göttingen, Georg-August-University, Göttingen 37099, Germany
[d] Department of Psychiatry and Psychotherapy, University Hospital, LMU Munich, Munich 80336, Germany
[e] International Max Planck Research School for Translational Psychiatry, Max Planck Institute of Psychiatry, Munich 80804, Germany
[f] Department of Psychiatry and Psychotherapy, Bezirkskrankenhaus Augsburg, Augsburg 86156, Germany
[g] Department of Psychiatry, Ruhr University Bochum, LWL University Hospital, Bochum 44791, Germany
[h] Department of Psychiatry, Klinikum Bremen-Ost, Bremen 28325, Germany
[i] Karl-Jaspers Clinic, European Medical School Oldenburg-Groningen, Oldenburg 26160, Germany
[j] Department of Psychiatry and Psychotherapeutic Medicine, Research Unit for Bipolar Affective Disorder, Medical University of Graz, Graz 8036, Austria
[k] Department of Psychiatry, Dr. Fontheim – Mental Health, Liebenburg 38704, Germany
[l] Department of Psychiatry and Psychotherapy, Agaplesion Diakonieklinikum, Rotenburg 27356, Germany
[m] Clinic for Psychiatry and Psychotherapy, Clinical Center Werra-Meißner, Eschwege 37269, Germany
[n] Asklepios Specialized Hospital, Göttingen 37081, Germany
[o] Psychiatric Hospital Lüneburg, Lüneburg 21339, Germany
[p] AMEOS Clinical Center Osnabrück, Osnabrück 49088, Germany
[q] ASKLEPIOS Specialized Hospital Tiefenbrunn, Rosdorf 37124, Germany
[r] Department of Psychiatry, Psychotherapy and Psychosomatics, Clinical Center Wilhelmshaven, Wilhelmshaven 26389, Germany
[s] Department of Psychiatry II, Ulm University, Bezirkskrankenhaus Günzburg, Günzburg 89312, Germany
[t] AMEOS Clinical Center Hildesheim, Hildesheim 31135, Germany
[u] Center for Systems Neuroscience (ZSN), Hannover 30559, Germany
[v] Department of Translational Psychiatry, Max Planck Institute of Psychiatry, Munich 80804, Germany
[w] Institute of Human Genetics, University of Bonn School of Medicine & University Hospital Bonn, Bonn 53127, Germany
[x] Department of Genomics, Life & Brain Center, University of Bonn, Bonn 53127, Germany
[y] Department of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim, University of Heidelberg, Mannheim 68159, Germany
[z] German Center for Neurodegenerative Diseases (DZNE), Göttingen 37075, Germany
[aa] iBiMED, Medical Sciences Department, University of Aveiro, Aveiro, Portugal

ARTICLE INFO

Article history:
Received 24 August 2018
Received in revised form 28 November 2018
Accepted 16 December 2018
Available online 3 January 2019

ABSTRACT

Background: Religious delusions are a common symptom in patients experiencing psychosis, with varying prevalence rates of religious delusions across cultures and societies. To enhance our knowledge of this distinct psychotic feature, we investigated the mutually-adjusted association of genetic and environmental factors with occurrence of religious delusions.
Methods: We studied 262 adult German patients with schizophrenia or schizoaffective disorder. Association with lifetime occurrence of religious delusions was tested by multiple logistic regression for the following putative

* Corresponding author.
E-mail address: heike.anderson-schmidt@med.uni-goettingen.de (H. Anderson-Schmidt).
[1] These authors contributed equally.
[2] Present address: mzBiostatistics, Statistical Consultancy, Göttingen, 37075, Germany.
[3] Present address: Burghof-Klinik Rinteln, Rinteln, 31737, Germany.

https://doi.org/10.1016/j.schres.2018.12.025
0920-9964/

Keywords:
Schizophrenia
Schizoaffective disorder
Religious delusions
Religious activity
Schizophrenia polygenic risk score

predictors: self-reported degree of religious activity, DSM-IV diagnosis, sex, age, education level, marital status, presence of acute delusion at the time of interview and an individual polygenic schizophrenia-risk score (SZ-PRS, available in 239 subjects).
Results: Of the 262 patients, 101 (39%) had experienced religious delusions. The risk of experiencing religious delusions was significantly increased in patients with strong religious activity compared to patients without religious affiliation (OR = 3.6, p = 0.010). Low or moderate religious activity had no significant effect. The same analysis including the SZ-PRS confirmed the effect of high religious activity on occurrence of religious delusions (OR = 4.1, p = 0.008). Additionally, the risk of experiencing religious delusions increased with higher SZ-PRS (OR 1.4, p = 0.020, using pT = 0.05 for SZ-PRS calculation). None of the other variables were significantly associated with lifetime occurrence of religious delusions.
Conclusions: Our results suggest that strong religious activity and high SZ-PRS are independent risk factors for the occurrence of religious delusions in schizophrenia and schizoaffective disorder.

1. Introduction

Religious delusions are a common symptom in patients with schizophrenia. They may be harder to treat than other delusions as they are generally held with more conviction (Appelbaum et al., 1999), thus being of high clinical relevance. Religious delusions occupy a special position as even though their content may overlap with other forms of delusions, such as grandiose delusions or delusions of guilt, they have an individual identity and are non-specific to a particular type of psychosis.

Religious delusions occur in between one-fifth and two-thirds of patients with delusions (Iyassu et al., 2014). The question arises as to what factors contribute to this substantial range in reported prevalence. While intercultural differences may give a partial explanation, it seems likely that individual sociodemographic variables, especially the extent of personal religiosity, as well as genetic factors may also play a role. It is therefore important to examine these factors further to better understand the phenomenon of religious delusions.

1.1. Influence of society

The observed prevalence of religious delusions in psychotic disorders differs across countries and cultures, and fluctuates over time (Atallah et al., 2001; Cannon and Kramer, 2012; Siddle et al., 2002a; Stompe et al., 1999). This is likely considerably due to changes in societal and cultural definitions of religiosity and consequently, religious delusions. In general, a delusion is defined as "a false belief based on incorrect inference about external reality that is firmly held despite what almost everyone else believes and despite what constitutes incontrovertible and obvious proof or evidence to the contrary. The belief is not ordinarily accepted by other members of the person's culture or subculture …" (DSM-5 glossary American Psychiatric Association, 2013, p. 819). Especially the latter, i.e. idiosyncrasy, is vital for distinguishing delusions with religious content from 'normal' religious faith (WHO, 1993). Based on this definition, one may expect religious delusions to be less common in very religious countries, as extreme religious beliefs may not be judged as delusions by society (Iyassu et al., 2014). However, in societies where religion plays an important role in everyday life, people with psychiatric disorders tend to show religious delusions more often than in non-religious societies (Siddle et al., 2002a). For example, prevalence rates of 63% of religious delusions in schizophrenia have been reported from Lithuania, (Rudalevičiene et al., 2008), compared to 24% in England (Siddle et al., 2002a), 21% in Germany/Austria (Tateyama et al., 1993), 17% in Turkey (Gecici et al., 2010), 13% in Taiwan (Huang et al., 2011), and 7% in Japan (Tateyama et al., 1993). According to polls from the time these studies were conducted (Eurobarometer poll, 2010), about 84% of Lithuanian, 41/51% of German/Austrian (ISSP, 1998) and 13% of Japanese citizens held some religious beliefs. These varying occurrence rates in different countries are not solely dependent on the importance of religion in that particular society but also on culture-specific themes of different religions that support certain mindsets associated with psychiatric pathology. For example, delusions of guilt in a religious context are much more frequent in Christian cultures compared to Judaism and Islam (Gearing et al., 2011).

1.2. Influence of individual religiosity

Not only cultural influences but also the association between personal religiosity and psychopathology of religious content in psychotic disorders remains unclear. On the one hand, strong individual religiosity may have negative effects. In moderately religious societies, schizophrenia patients with religious delusions were found to be more religious before illness onset than patients without these (Siddle et al., 2002b). Stronger religious activity of psychotic patients was also associated with higher symptom severity (Getz et al., 2001). Individuals who interpret symptoms like acoustic hallucinations in a religious context will probably seek medical help at a later point in time than non-religious ones (Moss et al., 2006; Siddle et al., 2002a) and may comply less with their medication (Kelly et al., 1987). On the other hand, a study from Lithuania (Rudalevičiene et al., 2008), a very religious society, found no association of individual religiosity with religious delusions, whereas sociodemographic factors such as higher education and being divorced were relevant. Furthermore, religious beliefs can help people affected by severe psychiatric illness like schizophrenia to cope better with their disorder and even improve prognoses (Flics and Herron, 1991; Tepper et al., 2001). Strong religiosity can also prevent suicide attempts and reduce the risk of substance abuse (Huguelet et al., 2007, 2009), most likely because these are often forbidden or considered sins in various religions.

1.3. Influence of genetics

It is yet unknown which genes are involved in the development of religiosity and if the same genes are implicated in the occurrence of religious delusions. About 40% of the variability in a person's religiosity appear to be heritable (Koenig et al., 2005; Vance et al., 2010). The vesicular monoamine transporter 2 (VMAT2) gene may be involved (Hamer, 2004). Results from a twin study by Hvidtjørn et al. (2013) indicate that social forms of religiosity, for instance church attendance, were more influenced by environmental factors whereas personal forms such as beliefs or prayer were more influenced by genetics. Religiosity associates with certain characteristics like concerns for community integration and existential certainty, suggesting that common heritable influences underlying such sentiments overlap with heritable influences underpinning religiosity (Lewis and Bates, 2013).

Genes that increase the risk for schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014) can be expected to influence the risk of experiencing delusions or other core symptoms of schizophrenia. Recently, an association between polygenic schizophrenia-risk scores (SZ-PRS) and the occurrence of psychotic

features has been demonstrated in schizophrenia and bipolar disorder (Bipolar disorder and Schizophrenia working group of the Psychiatric Genomics Consortium, 2018). Labbe et al. (2012) found different loci on chromosomes 9q and 2q to be associated with certain subgroups of delusions including such of religious content in schizophrenia.

To better understand the role of environmental and genetic factors underlying the occurrence of religious delusions, this study investigated the association of lifetime religious delusions with the self-reported degree of religious activity and individual polygenic schizophrenia-risk in a sample of German patients with schizophrenia or schizoaffective disorder. This investigation did not focus on genetic variants that specifically contribute to particular forms or contents of religious delusions.

2. Methods

2.1. Participants

290 adult in- and outpatients aged between 18 and 80 years with a lifetime diagnosis of paranoid schizophrenia or schizoaffective disorder were recruited across South, West and Northern Germany for the KFO241/PsyCourse cohort (Budde et al., 2018). Psychiatric diagnoses were established with a modified version of the Structured Clinical Interview for DSM-IV-TR Axis I Disorders (American Psychiatric Association, 2000; SCID-I, First et al., 2002), incorporating a review of previous medical records. The study protocol was approved by the local ethics committees and is in accordance with the 1964 Declaration of Helsinki. Informed written consent was obtained prior to study participation from all participants.

2.2. Materials

Patients' sociodemographic and clinical information were assessed using a comprehensive inventory for phenotype characterization. The manual contains a modified version of the SCID-I interview, including lifetime ratings of psychotic symptoms and lifetime occurrence of religious delusions, the Positive and Negative Syndrome Scale (PANSS, Kay et al., 1989) and a self-report questionnaire on religious activity (see supplement). Based on the answers of this questionnaire, patients were grouped into five categories: 1 = no religious affiliation, 2 = religious affiliation, not religiously active, 3 = religious affiliation, somewhat active, 4 = religious affiliation, moderately active, 5 = religious affiliation, very active. In patients with religious delusions, we classified the content of the delusions according to a scheme by Mundhenk (1999), a German hospital pastor working at a psychiatric clinic, who tried to categorize patients' religious delusions from a theological background. He identified 10 main themes of Christian religious delusions: 1) “God delusions” (delusions of being God), 2) “Jesus delusions” (being Jesus, the Messiah), 3) “Holy Spirit delusions”, 4) delusions of possession, 5) apocalyptic delusions, 6) grandiose delusions in the sense of being ‘chosen’, 7) delusions of guilt or being damned, 8) erotic religious delusions, 9) delusions of resurrection, 10) spontaneous associations (of religious symbols/meanings in things).

We calculated SZ-PRS with PLINK1.9 (https://www.cog-genomics.org/plink2, Purcell et al., 2007), incorporating imputed quality-controlled genome-wide patient genotypes (Illumina Infinium PsychArray). Imputation was performed with SHAPEIT/IMPUTE2 (Howie et al., 2009; Delaneau et al., 2013) with the 1000 Genomes Project phase3 integrated variant set as reference panel. Independent summary statistics of the large case-control genome-wide association study in schizophrenia (PGC study, Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014) were used to ascertain risk variants, their *p*-values, and associated odds ratios. For variants contributing to the SZ-PRS (PGC study p-values≤pT), the imputed dosage of the risk allele carried by an individual from this study was multiplied by the log (Odds Ratio) of that variant estimated in the PGC study. The resulting values were summed up, yielding SZ-PRS that rank individual polygenic schizophrenia risk robustly for a wide range of variant-inclusion thresholds pT (Dudbridge, 2013, see Supplementary Figure for details). Using a linkage-disequilibrium-pruned variant set shared with the PGC study, SZ-PRS were determined for n = 239 study patients, who clustered to 1000 Genomes Project European reference populations (EIGENSOFT principal component analysis, Price et al., 2006).

2.3. Statistical analyses

Out of 290 subjects, twenty-eight were excluded from analysis due to missing or unspecified sociodemographic variables (n = 14) or having a religious affiliation other than Christian (Islam: n = 9, other: n = 5). For the remaining 262 patients, association with lifetime occurrence of religious delusions as binary outcome was tested using a multiple logistic regression, considering as putative predictors the self-reported degree of religious activity, DSM-IV diagnosis, sex, age, education level, marital status, presence of acute delusion at the time of interview (PANSS- item P1 rated with a score of 2 or above), and the SZ-PRS (n = 239; exclusions: n = 11 not genotyped, n = 2 non-Caucasian European ancestry, $n = 10$ failed genotyping quality control). Conversely, we tested which of these variables associated with the self-reported degree of religious activity (ordinal outcome, tested by multiple ordinal logistic regression under the proportional odds assumption). Furthermore, univariate association tests between occurrence of religious delusions and all variables were performed using unpaired *t*-tests (age) or Fisher's exact test.

3. Results

Of the 262 patients (217 Christians, 45 without religious affiliation), 101 (39%) had experienced some kind of religious delusion(s) in their lives (see Fig. 1).

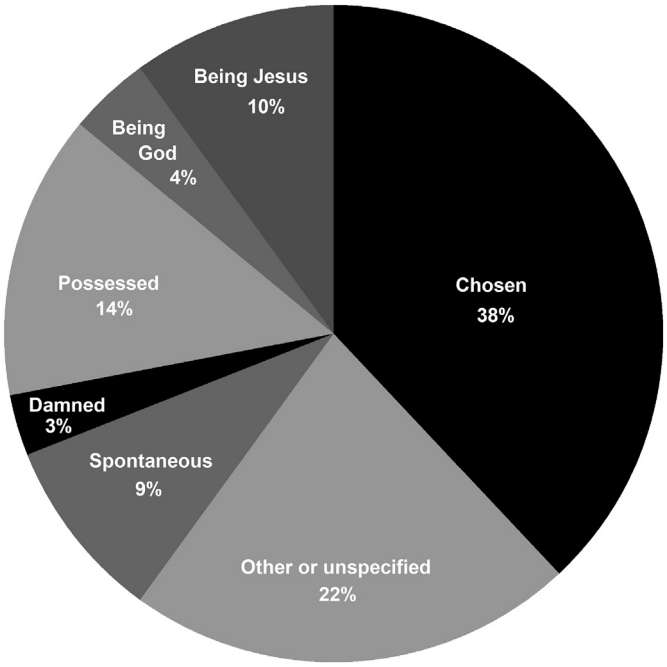

Fig. 1. Content of religious delusions Percentage of patients displaying subcategories of religious delusions according to the ten main themes of Christian religious delusions identified by Mundhenk (1999). Six categories were observed: n = 4 “God delusions” (delusions of being God), n = 10 “Jesus delusions” (being Jesus, the Messiah), n = 39 grandiose delusions in the sense of being ‘chosen’, n = 3 delusions of guilt or being damned, n = 14 delusions of possession, n = 9 spontaneous associations (of religious symbols/meanings in things). Four categories were not observed: “Holy Spirit delusions”, apocalyptic delusions, erotic religious delusions, delusions of resurrection. 22 patients did not fit these categories or had unspecified content.

Table 1
Occurrence of religious delusions.

	Religious delusions		Covariate-adjusted association test[a]	
	No (n = 161)	Yes (n = 101)		
Religious activity	n (%)	n (%)	OR	p-value
No religious affiliation	33 (20%)	12 (12%)	Reference group	
Religious affiliation, not active	33 (20%)	16 (16%)	1.2	0.675
Religious affiliation, somewhat active	51 (32%)	35 (35%)	1.7	0.182
Religious affiliation, moderately active	28 (17%)	19 (19%)	1.9	0.172
Religious affiliation, very active	16 (10%)	19 (19%)	3.6	0.010

	Religious delusions		Univariate association test[b]
	No (n = 161)	Yes (n = 101)	
Other sample characteristics	n (%)	n (%)	p-value
Diagnosis			1.000
Schizophrenia (DSM 295.30)	132 (82%)	83 (82%)	
Schizoaffective disorder (DSM 295.70)	29 (18%)	18 (18%)	
Sex			0.898
Male	96 (60%)	59 (58%)	
Female	65 (40%)	42 (42%)	
Age (mean ± SD, in years)	41 ± 13	40 ± 11	0.397
School education			0.101
No degree	4 (2%)	3 (3%)	
Basic degree	48 (30%)	19 (19%)	
Extended degree	45 (28%)	41 (41%)	
most advanced degree/A-levels	64 (40%)	38 (38%)	
Marital status			
Single	106 (66%)	70 (69%)	0.768
Married	27 (17%)	17 (17%)	
Divorced	28 (17%)	14 (14%)	
Acute delusions at time of interview[c]			1.000
Yes	91 (57%)	58 (57%)	
No	69 (43%)	43 (43%)	

[a] Lifetime occurrence of religious delusions contingent on the degree of religious activity (logistic regression, adjusted for the covariates diagnosis, sex, age, school education, marital status, and presence of acute delusions at time of interview). Odds ratios (OR) denote the risk of occurrence of religious delusion in subjects with various degrees of religious activity in relation to subjects with no religious affiliation.
[b] Fishers exact test (count data) or unpaired t-test (age).
[c] Missing values: 1 (acute delusion at time of interview).

89 patients thereof were Christian and 12 had no religious affiliation. According to Mundhenk's scheme, four patients were convinced to be God, another ten to be Jesus or the Messiah. Fourteen subjects thought they were possessed by the devil or some evil demon. Thirty-nine patients had experienced grandiose delusions of being 'chosen' by God or a higher power. Three patients thought they would be punished by God for their sins or be damned. Nine patients reported spontaneous religious associations. The content of religious delusions of the other twenty-two patients did not fit the categorization criteria by Mundhenk or had not been specified. No individual showed delusions of different subcategories at the same time. The full range of religious activity from none to very active was observed for Christian patients. Very active religious subjects had a 3.6 times higher risk of experiencing religious delusions compared to subjects without any religious affiliation ($p = 0.010$, covariate-adjusted logistic regression), while low or moderate religious activity had no significant influence (see upper part of Table 1 and Fig. 2).

Including SCZ-PRS in the model reduced the sample size to 239 subjects with available genetic data and Caucasian European ancestry. When adding adjustment for SZ-PRS, the association of high religious activity with occurrence of religious delusions remained (odds ratio [OR] = 4.1, $p = 0.008$, using $pT = 0.05$ for SZ-PRS calculation). Likewise, the risk of experiencing religious delusions was also higher with increasing SZ-PRS (OR = 1.4, $p = 0.020$ [$pT = 0.05$]) for an increase of the SZ-PRS by one sample standard deviation (see Fig. 3).

The association was robust with respect to the pT-value used for SZ-PRS calculation (Supplementary Figure panels A and C, $pT \geq 0.02$). The risk estimate of high religious activity was quite unaffected regarding SZ-PRS adjustment (Supplementary Figure panel B, dashed versus solid horizontal line). No other covariates were significantly associated with a lifetime occurrence of religious delusions, neither when mutually adjusted for in the logistic regression model nor in univariate tests (see Table 1). Conversely, the self-reported degree of religious activity was

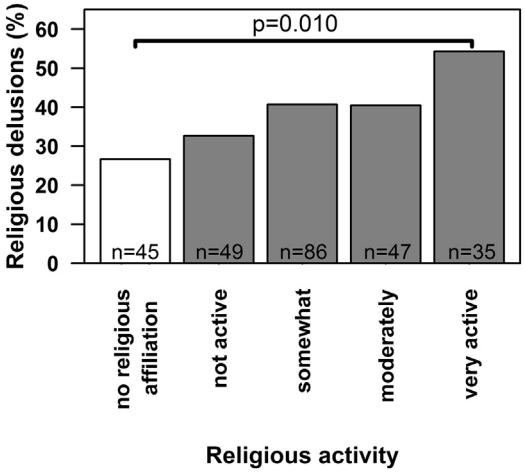

Fig. 2. Occurrence of religious delusions in schizophrenia and schizoaffective disorder is associated with strong religious activity Displayed are observed percentages of lifetime occurrence of religious delusion in subjects without religious affiliation (white bar) compared to religious subjects (grey bars; covariate-adjusted association $p = 0.010$, see the upper part of Table 1).

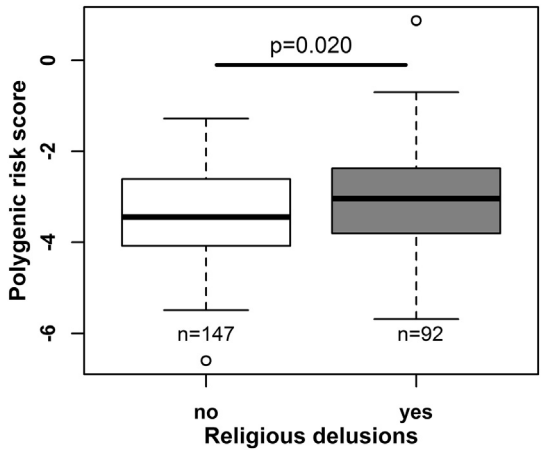

Fig. 3. Occurrence of religious delusions is associated with genetic predisposition for schizophrenia SZ-PRS were higher in patients who had experienced religious delusions (grey boxplot) compared to patients without religious delusions (white boxplot; significant covariate-adjusted group difference $p = 0.020$). SZ-PRS cumulated variants with substantial independent evidence for schizophrenia risk (variant-inclusion threshold $pT = 0.05$, $n = 239$ subjects with SZ-PRS).

higher in subjects who had experienced religious delusions ($p = 0.006$) compared to those without religious delusions and tended to be higher in women than men ($p = 0.073$, covariate-adjusted ordinal logistic regression). The other covariates were non-significant. Among the subgroup of patients with a lifetime occurrence of religious delusions, the acutely delusional patients (at the time of interview) did not score significantly higher on the self-rating scale of religious activity compared to the not acutely delusional ones ($p \geq 0.254$ for ordinal regression and logistic regression).

4. Discussion

Our data suggest that high personal religious activity and a high SZ-PRS are largely independent risk factors for the occurrence of religious delusions in patients with schizophrenia and schizoaffective disorder as the risk estimate for religious activity was quite unaffected regarding adjustment for SZ-PRS in our patient sample. High religious activity increased the likelihood of religious delusions occurring in our sample, consistent with some previous work (Getz et al., 2001; Peters et al., 1999). However, as prospective assessment of premorbid religiosity is not feasible, it remains unclear if high premorbid religiosity increases the probability of developing religious delusions after illness onset or if patients who experience religious delusions during illness episodes tend to devote themselves more to religion than they did before that experience (Koenig, 2007). Some studies have demonstrated that people with schizophrenia are in general more religious than healthy controls (Mohr et al., 2012). Nonetheless, while a positive attitude towards religion (Rosmarin et al., 2013) and moderate religious activity may aid to better cope with the disorder (Flics and Herron, 1991; Huguelet et al., 2007), very strong activity, particularly negative involvement, e.g. religious fanatism, could even be dangerous for some individuals. This may especially be the case for patients with a high genetic burden of schizophrenia-associated loci. Despite one not being directly linked with the other, the possibility remains that the expression of certain genes or transcript isoforms may get altered by environmental factors via epigenetic mechanisms.

The question arises why a higher SZ-PRS score was particularly associated with religious delusions. SZ-PRS derives its precision from the world-wide largest case-control study to date (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). It is unlikely that variants within the SZ-PRS or the score itself are specific for this particular type of delusion. Nonetheless, the occurrence of religious delusions may be an indicator of increased disorder severity. Schizophrenia patients with religious delusions have been shown to be more severely ill, i.e. have higher symptom scores, lower levels of functioning and higher doses of medication compared to patients with other types of delusions (Siddle et al., 2002a). Previously, researchers have mainly attributed this phenomenon to poorer treatment compliance due to patients' religious convictions. However, an additional biological component may exist. Assuming that religious delusions are a correlate of symptom severity, these may be more likely to occur in patients with a higher polygenic burden for the disorder, as higher PRS are expected to be associated with higher illness severity. Supporting this hypothesis, recent studies in first-episode psychosis patients showed that higher SZ-PRS predicted less improvement with antipsychotic drug treatment (Zhang et al., 2018). Other researchers found higher SZ-PRS to be significantly correlated with baseline (pre-treatment) symptoms, lower clinical global assessment of functioning (GAF), higher depressive symptoms and higher scores on a derived excitement factor of the PANSS (Santoro et al., 2018). Thus, we believe that the observed association between PRS and religious delusions in our study is indirect in nature and may be caused by a shared association with disorder severity.

4.1. Clinical implications

The results of this study have several important clinical implications. As a high level of personal religiosity was associated with a higher risk of religious delusions, this leaves clinicians with the dilemma of how to deal with strong religious activity in people with a known psychiatric disorder. Furthermore, drawing the line between 'normal' strong religiosity, 'hyperreligiosity', a symptom of psychopathology itself, and religious delusions may not always be a clear-cut decision. Rather, it appears that these concepts may represent different points on a spectrum of religiosity (Pechey and Halligan, 2011). Hyperreligiosity is not unique to psychiatric disorders but can also occur in neurological disorders, such as temporal lobe epilepsy or frontotemporal dementia. Functional imaging studies have shown that while there is some overlap in the brain regions involved in normal religious activity (Azari et al., 2001; Beauregard and Paquette, 2006), symptomatic hyperreligiosity (Bouman, 2011) and religious delusions (Puri et al., 2001), the activation patterns appear more widespread in normal religiosity.

As functional imaging techniques do not provide diagnostic certainty, distinguishing between different 'normal' and 'abnormal' forms of religiosity in psychiatric disorders remains the subjective decision of the treating clinician. To identify pathological forms of religiosity, it is crucial to investigate whether additional cognitive or behavioral abnormalities are present and if there was a shift in religious attitudes without external influences. Furthermore, sudden spontaneous religious conversion may serve as a potential warning sign for the development of 'pathological religiousness'.

In people who have already experienced psychotic symptoms, even 'normal' strong religious activity could act as a potentially dangerous trigger for developing religious delusions. This raises the question as to what recommendations regarding religious activities should be provided for these patients. Further research is needed to delve into these complex issues.

On the other hand, religiosity could also contribute to clinical therapy. In some trials, Christian or Muslim cognitive behavioral therapy (CBT) yielded better results than conventional CBT therapy for strongly religious patients (Weber and Pargament, 2014). Unfortunately, psychiatrists are more often atheists than other physicians (Neeleman and Persaud, 1995) and sometimes overtaxed when it comes to patients' spiritual questions. What complicates things further is that many spiritual teachers or leaders of religious communities are very skeptical about modern psychiatry. Although some attempts have already been made to establish collaborations between professional spiritual coaches and psychiatrists, prejudices from both sides can make it difficult to build a sustainable relationship between religious and psychiatric

mental health workers. However, to optimize the situation for religiously active psychiatric patients, strong collective efforts from both sides should be made in the future to proceed with this important aspect of mental health care.

4.2. Strengths and limitations

To our knowledge, our study is the first to investigate the connections between religious activity, genetic predisposition to schizophrenia and occurrence of religious delusions in schizophrenia and schizoaffective patients in Germany. As religiosity is a very subjective construct and was assessed by self-rating, how actively involved a person rates him- or herself may to some extent depend on that person's definition and concept. Nevertheless, gradual self-rating (see Supplement) has the advantage that it is intuitively applicable independent of religion or culture.

Another possible caveat of this study is that we jointly analyzed patients with schizophrenia and schizoaffective disorder for occurrence of religious delusions. In principle, it cannot be excluded that the delusions these patients suffer from may have different underlying properties depending on the diagnosis. For example, judging from clinical experience, manic patients often present with grandiose delusions even of religious content. However, statistical analyses were adjusted for diagnosis and diagnosis was not a significant factor. Furthermore, both diagnostic groups had the same probability of life-time occurrence of religious delusions (with 95% confidence interval: 38.6% ± 6.5% and 38.3% ± 13.9%).

Our sample may not represent the Eastern part of Germany, i.e. the former German Democratic Republic (GDR). Researchers have found lower prevalence rates of religious delusions in schizophrenia patients from the former GDR (East Germany) compared to West Germany (Pfaff et al., 2008). In the former GDR, religious activity was suppressed by the government over many years. Hence, the percentage of people considering themselves to be atheists is still significantly higher than in the Western part of Germany.

In contrast to previous studies, we decided not to subdivide the Christian subgroup of our patients further. The rationale for this was that we were unsure if Protestants, Catholics or Orthodox Christians were clearly aware of the differences between these three religious churches, especially individuals that stated to practice their religion 'not actively'. For many of these patients, it is likely that their ethnic and/or geographical background defined which Christian affiliation they belonged to. We also decided not to include patients with religious affiliations other than Christianity, as there were very few in our sample ($n = 14$).

Delusional content (Fig. 1) was categorized by religious topic, employing Mundhenk's scheme, which is tailored to the Christian affiliation. Categorizations of religious content are prone to be biased towards specific religions and may not cover all contents in a clear-cut manner. Clearly, more research on delusional content is warranted but is beyond the scope of this investigation.

4.3. Conclusions

Our data suggest that high personal religious activity and a high SZ-PRS are largely independent risk factors for the occurrence of religious delusions. A high level of religiosity appeared to increase the risk for developing religious delusions, which has important clinical implications. Further research is needed to examine the complex interplay between genetics, religiosity and religious delusions.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2018.12.025.

Contributors

Authors Katrin Gade, Dörthe Malzahn and Heike Anderson-Schmidt analyzed the data and wrote the manuscript. All other authors contributed to planning or conducting the recruitment, phenotyping and genotyping of patients. All authors contributed to the study design and data interpretation. All authors critically revised the manuscript and approved the final version.

Conflict of interest

There are no conflicts of interest to report.

Acknowledgement

We thank the interviewers Linda Gebel, Linus Wittmann, Silke Quast, Laura Filser, Lena Grüber, Michael Hamerle, Sophie Kirchner, Jana Nolden, Marianne Bärhold, Tina Bittel, Katharina Bachmann, Jaqueline Ohle, Kim Bartholdi, Sybille Schulz, Ida Haußleitner, Sandra Lorek, Svenja Mattausch, Milena Meyers, Barbara Nierste, Fabian Lang, Chadiga Aly, Judith Stöckel, Marlenna Pieper and Cosima Bitter, the lab team Uta Engelhardt, Anke Jahn-Brodmann, Verena Gullatz, Birgit Burde, Stefanie Behrens and all the study participants, without whom this work would not have been possible.

This research was funded by the Deutsche Forschungsgemeinschaft [DFG, grants: Klinische Forschergruppe (KFO) 241 and PsyCourse Consortium (SCHU 1603/5-1 & SCHU 1603/7-1;BI 576/5-1)]. Thomas G. Schulze was supported by the Dr. Lisa Oehler Foundation (Kassel, Germany). All funding sources had no further role in study design; in the collection, analysis and interpretation of the data; in writing the report; or in the decision to submit the paper for publication.

References

American Psychiatric Association, 2000. Diagnostic and Statistical Manual of Mental Disorders. 4th ed. (DSM-IV-TR). American Psychiatric Association, Washington, DC.

American Psychiatric Association, 2013. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. (DSM-5). American Psychiatric Association, Washington, DC.

Appelbaum, P.S., Robbins, P.C., Roth, L.H., 1999. Dimensional approach to delusions: comparison across types and diagnoses. Am. J. Psychiatry 156, 1938–1943.

Atallah, S.F., El-Dosoky, A.R., Coker, E.M., Nabil, K.M., El-Islam, M.F., 2001. A 22-year retrospective analysis of the changing frequency and patterns of religious symptoms among inpatients with psychotic illness in Egypt. Soc. Psychiatry Psychiatr. Epidemiol. 36, 407–415.

Azari, N.P., Nickel, J., Wunderlich, G., Niedeggen, M., Hefter, H., Tellmann, L., Herzog, H., Stoerig, P., Birnbacher, D., Seitz, R.J., 2001. Neural correlates of religious experience. Eur. J. Neurosci. 13, 1649–1652.

Beauregard, M., Paquette, V., 2006. Neural correlates of a mystical experience in Carmelite nuns. Neurosci. Lett. 405, 186–190.

Bipolar disorder and Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2018. Genomic dissection of bipolar disorder and schizophrenia, including 28 subphenotypes. Cell 173 (7), 1705–1715.

Bouman, D., 2011. The Neurobiological Basis of Hyperreligiosity. (Bachelor thesis in Cognitive Neuroscience). Tilburg University, the Netherlands Retrieved from. http://arno.uvt.nl/show.cgi?fid=114836.

Budde, M., Anderson-Schmidt, H., Gade, K., et al., 2018. A longitudinal approach to biological psychiatric research: the PsyCourse study. Am. J. Med. Genet. B Neuropsychiatr. Genet. 00, 1–14. https://doi.org/10.1002/ajmg.b.32639.

Cannon, B.J., Kramer, L.M., 2012. Delusion content across the 20th century in an American psychiatric hospital. Int. J. Soc. Psychiatry 58, 323–327.

Delaneau, O., Zagury, J.F., Marchini, J., 2013. Improved whole-chromosome phasing for disease and population genetic studies. Nat. Methods 10 (1), 5–6.

Dudbridge, F., 2013. Power and predictive accuracy of polygenic risk scores. PLoS Genet. 9 (3), e1003348.

First, M.B., Spitzer, R.L., Gibbon, M., Williams, J.B.W., 2002. Structured Clinical Interview for DSM-IV-TR Axis I Disorders Research Version, Patient Edition with Psychotic Screen (SCID-I/P). Biometrics Research, New York State Psychiatric Institute, New York.

Flics, D.H., Herron, W.G., 1991. Activity - withdrawal, diagnosis, and demographics as predictors of premorbid adjustment. J. Clin. Psychol. 47, 189–198.

Gearing, R.E., Alonzo, D., Smolak, A., McHugh, K., Harmon, S., Baldwin, S., 2011. Association of religion with delusions and hallucinations in the context of schizophrenia: implications for engagement and adherence. Schizophr. Res. Mar. 126 (1–3), 150–163.

Gecici, O., Kuloglu, M., Ozkan, G., Ozbulut, O., Kurt, E., Onen, S., Ekinci, O., Yesilbas, D., Caykoylu, A., Emul, M., Atlatas, M., Albayrak, Y., 2010. Phenomenology of delusions and hallucinations in schizophrenia by religious convictions. Bull. Clin. Psychopharmacol. 13, 245–259.

Getz, G.E., Fleck, D.E., Strakowski, S.M., 2001. Frequency and severity of religious delusions in Christian patients with psychosis. Psychiatry Res. 103, 87–91.

Hamer, D., 2004. The God Gene: How Faith Is Hardwired into our Genes. Random House Inc., New York, USA.

Howie, B.N., Donnelly, P., Marchini, J., 2009. A flexible and accurate genotype imputation method for the next generation of genome-wide association studies. PLoS Genet. 5 (6), e1000529.

Huang, C.L.C., Shang, C.Y., Shieh, M.S., Lin, H.N., Su, J.C.J., 2011. The interactions between religion, religiosity, religious delusion/hallucination, and treatment-seeking behavior among schizophrenic patients in Taiwan. Psychiatry Res. 187, 347–353.

Huguelet, P., Mohr, S., Jung, V., Gillieron, C., Brandt, P.Y., Borras, L., 2007. Effect of religion on suicide attempts in outpatients with schizophrenia or schizo-affective disorders compared with inpatients with non-psychotic disorders. Eur. Psychiatry 22, 188–194.

Huguelet, P., Borras, L., Gillieron, C., Brandt, P.-Y., Mohr, S., 2009. Influence of spirituality and religiousness on substance misuse in patients with schizophrenia or schizo-affective disorder. Subst. Use Misuse 44, 502–513.

Hvidtjørn, D., Petersen, I., Hjelmborg, J., Skytthe, A., Christensen, K., Hvidt, N., 2013. Familial resemblance in religiousness in a secular society: a twin study. Twin Res. Hum. Genet. 16 (2), 544–553.
ISSP, Research Group, 1998. International Social Survey Programme: Religion II - ISSP 1998.
Iyassu, R., Jolley, S., Bebbington, P., Dunn, G., Emsley, R., Freeman, D., Fowler, D., Hardy, A., Waller, H., Kuipers, E., Garety, P., 2014. Psychological characteristics of religious delusions. Soc. Psychiatry Psychiatr. Epidemiol. 49, 1051–1061.
Kay, S.R., Opler, L.A., Lindenmayer, J.P., 1989. The positive and negative syndrome scale (PANSS): rationale and standardisation. Br. J. Psychiatry Suppl. Nov (7), 59–67.
Kelly, G.R., Mamon, J. a, Scott, J.E., 1987. Utility of the health belief model in examining medication compliance among psychiatric outpatients. Soc. Sci. Med. 25, 1205–1211.
Koenig, H.G.H., 2007. Religion, spirituality and psychotic disorders. Rev. Psiquiatr. Clin. 34, 40–48.
Koenig, L.B., McGue, M., Krueger, R.F., Bouchard, T.J., 2005. Genetic and environmental influences on religiousness: findings for retrospective and current religiousness ratings. J. Pers. 73, 471–488.
Labbe, A., Bureau, A., Moreau, I., Roy, M.-A., Chagnon, Y., Maziade, M., Merette, C., 2012. Symptom dimensions as alternative phenotypes to address genetic heterogeneity in schizophrenia and bipolar disorder. Eur. J. Hum. Genet. 20, 1182–1188.
Lewis, G.J., Bates, T.C., 2013. Common genetic influences underpin religiosity, community integration, and existential uncertainty. J. Res. Pers. 47, 398–405.
Mohr, S., Borras, L., Nolan, J., Gillieron, C., Brandt, P.-Y., Eytan, A., Leclerc, C., Perroud, N., Whetten, K., Pieper, C., Koenig, H.G., Huguelet, P., 2012. Spirituality and religion in outpatients with schizophrenia: a multi-site comparative study of Switzerland, Canada, and the United States. Int. J. Psychiatry Med. 44, 29–52.
Moss, Q., Fleck, D.E., Strakowski, S.M., 2006. The influence of religious affiliation on time to first treatment and hospitalization. Schizophr. Res. 84, 421–426.
Mundhenk, R., 1999. Sein wie Gott. Aspekte des Religiösen im schizophrenen Erleben und Denken. Paranus Verlag, Neumünster.
Neeleman, J., Persaud, R., 1995. Why do psychiatrists neglect religion? Br. J. Med. Psychol. 68, 169–178.
Pechey, R., Halligan, P., 2011. The prevalence of delusion-like beliefs relative to sociocultural beliefs in the general population. Psychopathology 44, 106–115.
Peters, E., Day, S., Mckenna, J., Orbach, G., 1999. Delusional ideation in religious and psychotic populations. Br. J. Clin. Psychol. 38, 83–96.
Pfaff, M., Quednow, B.B., Brüne, M., Juckel, G., 2008. Schizophrenia and religiousness–a comparative study at the time of the two German states. Psychiatr. Prax. 35, 240–246.
Price, A.L., Patterson, N.J., Plenge, R.M., Weinblatt, M.E., Shadick, N.A., Reich, D., 2006. Principal components analysis corrects for stratification in genome-wide association studies. Nat. Genet. 38 (8), 904–909.
Purcell, S., Neale, B., Todd-Brown, K., Thomas, L., Ferreira, M.A., Bender, D., Maller, J., Sklar, P., de Bakker, P.I., Daly, M.J., Sham, P.C., 2007. PLINK: a tool set for whole-genome association and population-based linkage analyses. Am. J. Hum. Genet. 81 (3), 559–575.
Puri, B.K., Lekh, S.K., Nijran, K.S., Bagary, M.S., Richardson, A.J., 2001. SPECT neuroimaging in schizophrenia with religious delusions. Int. J. Psychophysiol. 40, 143–148.
Rosmarin, D.H., Bigda-Peyton, J.S., Öngur, D., Pargament, K.I., Björgvinsson, T., 2013. Religious coping among psychotic patients: relevance to suicidality and treatment outcomes. Psychiatry Res. 210, 182–187.
Rudalevičiene, P., Stompe, T., Narbekovas, A., Raŝkauskiene, N., Bunevičius, R., 2008. Are religious delusions related to religiosity in schizophrenia? Medicina (B. Aires). 44, 529–535.
Santoro, M.L., Ota, V., de Jong, S., Noto, C., Spindola, L.M., Talarico, F., Gouvea, E., Lee, S.H., Moretti, P., Curtis, C., Patel, H., Newhouse, S., Carvalho, C.M., Gadelha, A., Cordeiro, Q., Bressan, R.A., Belangero, S.I., Breen, G., 2018. Polygenic risk score analyses of symptoms and treatment response in an antipsychotic-naive first episode of psychosis cohort. Transl. Psychiatry 8 (1), 174. https://doi.org/10.1038/s41398-018-0230-7.
Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014. Biological insights from 108 schizophrenia-associated genetic loci. Nature 511 (7510), 421–427.
Siddle, R., Haddock, G., Tarrier, N., Faragher, E.B., 2002a. Religious delusions in patients admitted to hospital with schizophrenia. Soc. Psychiatry Psychiatr. Epidemiol. 37, 130–138.
Siddle, R., Haddock, G., Tarrier, N., Faragher, E.B., 2002b. The validation of a religiosity measure for individuals with schizophrenia. Ment. Health Relig. Cult. 5, 267–284.
Special Eurobarometer Biotechnology Report, 2010. 341/Wave 73.1 – TNS Opinion and Social, Brussels.
Stompe, T., Friedman, A., Ortwein, G., Strobl, R., Chaudhry, H.R., Najam, N., Chaudhry, M.R., 1999. Comparison of delusions among schizophrenics in Austria and in Pakistan. Psychopathology 32, 225–234.
Tateyama, M., Asai, M., Kamisada, M., Hashimoto, M., Bartels, M., Heimann, H., 1993. Comparison of schizophrenic delusions between Japan and Germany. Psychopathology 26, 151–158.
Tepper, L., Rogers, S.A., Coleman, E.M., Malony, H.N., 2001. The prevalence of religious coping among persons with persistent mental illness. Psychiatr. Serv. 52, 660–665.
Vance, T., Maes, H.H., Kendler, K.S., 2010. Genetic and environmental influences on multiple dimensions of religiosity: a twin study. J. Nerv. Ment. Dis. 198 (10), 755–761.
Weber, S.R., Pargament, K.I., 2014. The role of religion and spirituality in mental health. Curr. Opin. Psychiatry 27, 358–363.
WHO, 1993. ICD-10 Classification of Mental and Behavioral Disorders. Diagnostic Criteria for Research. World Heal. Organ, Geneva.
Zhang, J.P., Robinson, D., Yu, J., Gallego, J., Fleischhacker, W.W., Kahn, R.S., Crespo-Facorro, B., Vazquez-Bourgon, J., Kane, J.M., Malhotra, A.K., Lencz, T., 2018. Polygenic risk score as a predictor of antipsychotic efficacy in first-episode psychosis. Am. J. Psychiatry https://doi.org/10.1176/appi.ajp.2018.17121363 (Epub ahead of print).