



**HAL**  
open science

## Activation of the left medial temporal gyrus and adjacent brain areas during affective theory of mind processing correlates with trait schizotypy in a nonclinical population

Ksenija Vucurovic, Delphine Raucher-Chéné, Alexandre Obert, Pamela Gobin, Audrey Henry, Sarah Barrière, Martina Traykova, Fabien Gierski, C. Portefaix, Stéphanie Caillies, et al.

### ► To cite this version:

Ksenija Vucurovic, Delphine Raucher-Chéné, Alexandre Obert, Pamela Gobin, Audrey Henry, et al.. Activation of the left medial temporal gyrus and adjacent brain areas during affective theory of mind processing correlates with trait schizotypy in a nonclinical population. *Social Cognitive and Affective Neuroscience*, 2023, 18 (1), pp.nsac051. 10.1093/scan/nsac051 . hal-03780960

**HAL Id: hal-03780960**

**<https://hal.science/hal-03780960v1>**

Submitted on 24 Sep 2024

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution 4.0 International License

# Activation of the left medial temporal gyrus and adjacent brain areas during affective theory of mind processing correlates with trait schizotypy in a nonclinical population

Ksenija Vucurovic,<sup>1,2</sup> Delphine Raucher-Chéné,<sup>1,3,4</sup> Alexandre Obert,<sup>5</sup> Pamela Gobin,<sup>1,3</sup> Audrey Henry,<sup>1,3</sup> Sarah Barrière,<sup>3</sup> Martina Traykova,<sup>3</sup> Fabien Gierski,<sup>1,3,6</sup> Christophe Portefaix,<sup>7,8</sup> Stéphanie Caillies,<sup>1</sup> and Arthur Kaladjian<sup>1,3,9</sup>

<sup>1</sup>Université de Reims Champagne Ardenne, Laboratoire Cognition, Santé, Société, EA 6291, 51100 Reims, France

<sup>2</sup>Centre Rémois de Psychothérapie et Neuromodulation, 51100 Reims, France

<sup>3</sup>Pôle Universitaire de Psychiatrie, EPSM et CHU de Reims, 51100 Reims, France

<sup>4</sup>McGill University, Douglas Mental Health University Institute, 11290 Montreal, Canada

<sup>5</sup>Champollion National University Institute, Cognition Sciences, Technology & Ergonomics Laboratory, University of Toulouse, 81000 Albi, France

<sup>6</sup>INSERM U1247 GRAP, Research Group on Alcohol and Drugs, Université de Picardie Jules Verne, 80000 Amiens, France

<sup>7</sup>Radiology Department, Reims University Hospital, 51100 Reims, France

<sup>8</sup>University of Reims Champagne-Ardenne, CRSTIC Laboratory, 51100 Reims, France

<sup>9</sup>University of Reims Champagne-Ardenne Faculty of Medicine, 51100 Reims, France

Correspondence should be addressed to Ksenija Vucurovic, Laboratoire Cognition, Santé, Société (C2S - EA 6291), UFR Lettres et Sciences Humaines, 57 rue Pierre Taittinger, Reims Cedex 51096, France. E-mail: [kvucurovic@chu-reims.fr](mailto:kvucurovic@chu-reims.fr)

## Abstract

Schizophrenia, a severe psychiatric disorder, is associated with abnormal brain activation during theory of mind (ToM) processing. Researchers recently suggested that there is a continuum running from subclinical schizotypal personality traits to fully expressed schizophrenia symptoms. Nevertheless, it remains unclear whether schizotypal personality traits in a nonclinical population are associated with atypical brain activation during ToM tasks. Our aim was to investigate correlations between fMRI brain activation during affective ToM (ToMA) and cognitive ToM (ToMC) tasks and scores on the Schizotypal Personality Questionnaire (SPQ) and the Basic Empathy Scale in 39 healthy individuals. The total SPQ score positively correlated with brain activation during ToMA processing in clusters extending from the left medial temporal gyrus (MTG), lingual gyrus and fusiform gyrus to the parahippocampal gyrus (Brodmann area: 19). During ToMA processing, the right inferior occipital gyrus, right MTG, precuneus and posterior cingulate cortex negatively correlated with the emotional disconnection subscore and the total score of self-reported empathy. These posterior brain regions are known to be involved in memory and language, as well as in creative reasoning, in nonclinical individuals. Our findings highlight changes in brain processing associated with trait schizotypy in nonclinical individuals during ToMA but not ToMC processing.

**Key words:** fMRI; schizophrenia; social cognition; schizotypy; CHR; psychosis proneness

## Introduction

Schizophrenia is a severe and often debilitating neurodevelopmental disorder that arises from an interaction between genetic and environmental factors (Kahn et al., 2015). A wide range of cognitive deficits have been reported in patients (Catts et al., 2013). It was in a bid to account for these complex cognitive deficits and their underlying neurobiological correlates in schizophrenia that the concept of schizophrenia spectrum disorder was developed, suggesting that the full-blown disease is only the most severe form (Guloksuz and Van Os, 2018). Converging evidence indicates that vulnerability to schizophrenia is expressed across a dynamic

continuum referred to as schizotypy (Barrantes-Vidal et al., 2014).

Schizotypy can be defined as a set of personality traits leading to a variety of cognitive, emotional and social behaviors that are often perceived by others to be unusual (Cohen et al., 2015). It has been suggested that schizotypy is highly heritable (Romero-Garcia et al., 2020), is normally distributed in the general population (Nelson et al., 2013) and ranges from subclinical manifestations like social eccentricity and unusual beliefs (Cohen et al., 2015) to clinical manifestations of schizotypal personality disorder (Bora and Baysan Arabaci, 2009; Ettinger et al., 2014). Schizotypy is a multidimensional construct (Raine, 1991; Stefanis et al., 2004;

Received: 25 May 2021; Revised: 31 July 2022; Accepted: 13 September 2022

© The Author(s) 2023. Published by Oxford University Press.

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<https://creativecommons.org/licenses/by/4.0/>), which permits unrestricted reuse, distribution, and reproduction in any medium, provided the original work is properly cited.

Barrantes-Vidal *et al.*, 2013), with its positive and negative dimensions being most consistently replicated (Cohen *et al.*, 2015) using a variety of assessment instruments. The Schizotypal Personality Questionnaire (SPQ) is widely used to assess trait schizotypy in nonclinical individuals (Raine, 1991), even though there has been a debate about its factor structure across cultures, with three-factor (Raine *et al.*, 1994; Dumas *et al.*, 2000; Wuthrich and Bates, 2006), four-factor (Compton *et al.*, 2009) and even five-factor (Chmielewski and Watson, 2008) models being reported. The SPQ was validated in a sample of French adults as a three-factor model (Dumas *et al.*, 2000).

The prevalence of schizotypy, defined as an expression of schizotypal personality traits, is estimated to be close to 10% (Nelson *et al.*, 2013). From the perspective of evolutionary psychiatry, this high prevalence can be viewed in terms of selective advantage (Burns, 2006). For example, some authors have suggested that creativity, defined as the ability to produce an original, innovative and context-appropriate production (Suddendorf and Fletcher-Flinn, 1997), is a potential advantage conferred by schizotypal personality traits (Park *et al.*, 2015), especially the positive dimension of schizotypy (Jacquet *et al.*, 2020; McDonald *et al.*, 2021). Furthermore, schizotypy and creativity may have a shared neural basis (Fink *et al.*, 2014). Some individuals with trait schizotypy report high subjective well-being (Goulding, 2004) and invest more in leisure and creative activities, where they can excel by expressing their high level of creativity (Nelson and Rawlings, 2010). It has been suggested that individuals with marked schizotypal traits are only at risk of developing schizophrenia if they are exposed to additional risk factors (Morton *et al.*, 2017).

Schizotypy therefore provides a useful construct for studying the development of schizophrenia spectrum psychopathology, including neuroimaging markers of the disease (Nelson *et al.*, 2013). In addition, it has been suggested that schizotypy could serve as a framework for studying social cognition mechanisms in nonclinical individuals (i.e. outside the pathological context), in terms of adaptation and evolution (Cohen *et al.*, 2015).

Social cognition can be defined as the set of cognitive processes that allow individuals to understand the behaviors of others and adapt well to complex social environments (Martin *et al.*, 2014). Theory of mind (ToM) is one of the central processes of social cognition defined by the Social Cognition Psychometric Evaluation initiative (Pinkham *et al.*, 2014) and refers to the ability to attribute mental states (e.g. thoughts, beliefs, intentions and emotions) to others.

A distinction has recently been made between affective ToM (ToMA) and cognitive ToM (ToMC) at both the behavioral (Dennis *et al.*, 2013) and neural levels (Sebastian *et al.*, 2012; Bodden *et al.*, 2013; Schlaffke *et al.*, 2015). ToMC can be defined as the ability to infer the epistemic mental states of others (beliefs, knowledge or intentions) without any emotional connotation (Sebastian *et al.*, 2012). ToMA can be defined as the ability to theorize about the emotional states of others in a social context (Bensalah *et al.*, 2016).

The distinction between ToMA and ToMC brings into play the concept of empathy (Wellman and Liu, 2004; Bensalah *et al.*, 2016). Empathy is a complex neuropsychological process that enables the emotions of others to be shared, understood and responded to in a socially appropriate manner (Narme *et al.*, 2010). Three components of empathy can be identified: affective, cognitive and behavioral (Bensalah *et al.*, 2016). Emotional empathy corresponds to the process of emotional contagion, whereby the emotions of others are shared via an automatic mechanism of isomorphic

emotion arousal (Narme *et al.*, 2010; Dennis *et al.*, 2013). Cognitive empathy involves processes of affective perspective-taking and emotional disconnection (Carré *et al.*, 2013; Bensalah *et al.*, 2016; Vucurovic *et al.*, 2020). Emotional disconnection refers to the ability to detach oneself from the emotions aroused by emotional contagion, whereas ToMA involves reasoning about the emotions of others. Cognitive empathy and ToMA are therefore conceptually close processes that share affective perspective-taking (Bensalah *et al.*, 2016). Finally, behavioral empathy consists in developing the social behavior most suited to the situation (Bensalah *et al.*, 2016), such as going to console a crying child. These three processes interact dynamically in individuals' reactions to the emotional states of others (Narme *et al.*, 2010).

Impaired ToM performances have been described in schizotypy on a behavioral level (Bohec *et al.*, 2021) and in terms of brain activation during ToM tasks (Modenato and Draganski, 2015; Leung *et al.*, 2021). Results are particularly striking when high levels of schizotypal personality traits are expressed in individuals (Bora, 2020). Data from individuals at clinically high risk of schizophrenia and schizotypy suggest that ToM deficits are a holistic marker of schizophrenia spectrum disorder (Nelson *et al.*, 2013). A behavioral study conducted among a sample of nonclinical individuals with high SPQ scores found that their ToMA performances were significantly impaired, compared with those of individuals with low schizotypy traits, whereas the two groups had comparable ToMC performances (Kocsis-Bogár *et al.*, 2017).

Impaired social functioning in schizophrenia correlates with abnormal activation of the mentalizing network (Mohnke *et al.*, 2014; Kronbichler *et al.*, 2017; Jáni and Kašpárek, 2018), and several neuroimaging studies have shown that in schizophrenia there is a decrease in volume (Raucher-Chéné *et al.*, 2020) or metabolism (Dodell-Feder *et al.*, 2014; Bitsch *et al.*, 2021) in the mentalizing brain areas that are observed from the very first episode of psychosis (Bartholomeusz *et al.*, 2018). It was also suggested that impaired brain activation during mentalizing could be genetically influenced and may constitute an intermediate phenotype of psychosis (Gottesman and Gould, 2003). Recent coordinate-based meta-analyses suggested abnormal brain activation during mentalizing in individuals with a clinical high risk for schizophrenia as well (Vucurovic *et al.*, 2021). Therefore, a better understanding of brain processing during ToM in schizophrenia spectrum disorders, in particular in schizotypy-trait individuals, would help us to identify potential therapeutic targets in schizophrenia.

To our knowledge, the neural correlates of ToMA and ToMC have not yet been explored in relation to schizotypal personality traits in the general population. The aim of the present study was therefore to explore the neural correlates of schizotypal traits in nonclinical participants, while they performed a ToMA and ToMC task. We also aimed to investigate the correlation between brain activation and self-reported empathy, in order to identify how emotion-related processing of the social context might be associated with schizotypal traits. Due to the original nature of the present study, it remains difficult to state finer hypotheses. However, considering the literature, we predicted that the schizotypy dimension would be correlated with the activation of regions previously reported to be abnormally activated in schizophrenia, namely the medial prefrontal cortex (mPFC), bilateral temporoparietal junction, superior temporal gyrus and precuneus. We also expected that self-reported empathy scores would be correlated with brain activation during ToMA processing.

## Materials and methods

### Ethical statement

This study was approved by the regional ethics committee (registered under no. ID-RCB 2016-A00275-46). It was carried out in accordance with the Declaration of Helsinki, and all participants gave their written informed consent prior to being included in the study. The study was also preregistered in ClinicalTrials.gov (NCT02834182). All participants received compensation of 70 euros for their time and travel expenses.

### Participants

Here, we aimed to explore brain activation correlation with a clinical score of SPQ (trait schizotypy). Because there is a lack of available published data on this topic, it was unlikely to reliably estimate the number of participants to include before the study. Based on the data of similar design that obtain statistically significant results (Wang et al., 2015; Lech et al., 2016), we recruited 45 healthy individuals through advertisements in the local community. Six participants were not included in the study, two because the SPQ scale was not completed correctly and four due to functional magnetic resonance imaging (fMRI) artifacts. All participants were right-handed native French speakers with normal or corrected-to-normal hearing and vision. They had no history of neurological or psychiatric disorder according to the diagnostic and statistical manual of mental disorders 5th edition (DSM-5) (American Psychological Association, 2013) or MRI contraindication (i.e. cardiac pacemaker or other metallic implants). Participants were screened for eligibility by trained psychiatrists. The absence of a current or lifetime severe psychiatric disorder was corroborated by the Mini-International Neuropsychiatric Interview (Sheehan et al., 1998).

### Experimental design

Trait schizotypy was measured with the SPQ (Raine, 1991). This 74-item self-report true-false questionnaire was originally developed to measure the nine factors of schizotypy defined by the DSM-III-R. However, a subsequent factor analytical study in an adult French population suggested that the results could be presented along just three dimensions: cognitive-perceptual, reflecting positive symptoms; interpersonal, reflecting negative symptoms; and disorganized (Dumas et al., 2000). All participants completed the self-report Basic Empathy Scale (BES; Carré et al., 2013).

### Experimental task

We used a previously validated cartoon task to comparatively explore ToMA and ToMC during a scanning procedure (Sebastian et al., 2012).

Briefly, participants are shown a series of 30 vignette stories. For each one, they have to build a theory about the protagonists' feelings (ToMA; 10 stories), the protagonists' intentions (ToMC; 10 stories) or physical causality (PC; requiring an understanding of the relationship between objects, but no mental state inference; 10 stories). Each story is composed of three pictures showing two protagonists who are each introduced to the participant. Participants have to respond to the question 'What is the end of the story?' by deciding which of the two pictures displayed on the final screen depicts the most appropriate ending.

### fMRI analyses

The task was implemented in E-Prime 2.0 (Psychology Software Tools, Inc.) for presentation purposes and organized in a

block design. Data were acquired using a Siemens 3T MRI scanner with a 20-channel head-neck coil. For each participant, a T1-weighted structural image parallel to the AC-PC line with a tilt of  $-30^\circ$  was acquired with the following parameters: TR = 2800 ms, TE = 6 ms, flip angle =  $27^\circ$ , 36 slices, slice thickness = 4.5 mm, no gap, matrix =  $256 \times 256$ , FOV  $240 \times 240 \text{ mm}^2$  and acquisition voxel size =  $0.98 \times 0.98 \times 4.5 \text{ mm}^3$ . Functional data were acquired with multislice T2\*-weighted echoplanar volumes with BOLD contrast. The sequence used the following acquisition parameters: 36 slices acquired using an interleaved ascending direction, same axial plane as the T1 sequence, TR = 2000 ms, TE = 30 ms, flip angle =  $90^\circ$ , slice thickness = 4.5 mm, no gap, matrix =  $80 \times 80$ , FOV =  $240 \times 240 \text{ mm}^2$  and acquisition voxel size =  $3 \times 3 \times 4.5 \text{ mm}^3$ . Functional data were acquired during a single run of 12 min, with 352 acquired volumes.

Imaging data were analyzed using Statistical Parametric Mapping 12th edition (SPM12) ([www.fil.ion.ucl.ac.uk/spm](http://www.fil.ion.ucl.ac.uk/spm)) implemented in Matlab 2016. The first six functional image volumes were discarded to allow for T1 equilibration effects. Images were spatially realigned to the mean functional image of the series. A slice-timed correction was applied. Potential outlier scans were detected using Artifact Detection Tools algorithms. Scans showing a global BOLD signal more than five standard deviations from the mean were marked as outliers and included as nuisance regressors in first-level design matrices. Images were directly segmented and normalized to the standard anatomical space of the Montreal Neurological Institute (MNI). Resample resolution was set at  $2 \text{ mm} \times 2 \text{ mm} \times 2 \text{ mm}$ . Finally, spatial smoothing was performed with an isotropic three-dimensional Gaussian filter with a full width at half maximum of 4 mm.

First-level analyses were conducted with a modeled regressor of the three conditions: ToMA, ToMC and PC. Visual fixations and the instruction screen were modeled as variables of no interest. The realignment parameters took account of variance resulting from head movement. Data were high-pass filtered at 128 Hz to remove low-frequency drifts.

At the first level, four contrasts of interest were conducted for each participant: ToMA > PC, ToMC > PC, ToMA > ToMC and ToMC > ToMA. The resulting first-level images were then entered into separate one-sample t-tests in second-level analyses. Results were thresholded at  $k = 20$  contiguous voxels and  $P < 0.05$  family-wise error (FWE)-corrected. Furthermore, correlational analyses were performed for each contrast of interest, including the total SPQ score as a covariate in the regression model. Results were thresholded at  $k = 20$  contiguous voxels and  $P < 0.001$ . Analyses were restricted to voxels included in the mean gray matter mask calculated from individual gray matter images. Clusters of significant activation were labeled using the Automated Anatomical Labeling (AAL) toolbox (Rolls et al., 2015). Significant clusters were then used in Region Of Interest (ROI) analyses. Thus, the mean activation for each contrast and cluster was extracted using the REX toolbox (<https://www.nitrc.org/projects/rex/>) and entered into Spearman's correlational analyses with (i) SPQ score and subscores and (ii) BES score and subscores. All statistical analyses of behavioral data were performed using Jeffreys's Amazing Statistics Program (JASP) (Version 0.14.1) computer software with a threshold set at  $P = 0.05$ .

## Results

### Behavioral data

Participants' characteristics and SPQ and BES scores are set out in Table 1.

**Table 1.** Participants' characteristics

	N = 39	
	M	(s.d.)
Age in years	39.51	(12.45)
Education level in years	12.33	(2.08)
BES total score	77.79	(7.59)
– Emotional contagion	19.41	(4.75)
– Cognitive empathy	33.03	(2.77)
– Emotional disconnection	25.36	(3.22)
SPQ total score		
– Negative (interpersonal)		
– Positive (cognitive/perceptual)		
– Disorganized	8.74	(7.54)
	3.85	(4.26)
	2.38	(2.70)
	2.51	(2.50)

Concerning task performance, the mean response accuracy was 93.59% for ToMA (s.d. = 25.53, range = 60–100), 96.67% for ToMC (s.d. = 17.97, range = 80–100) and 93.08% for PC (s.d. = 25.42, range = 60–100). There was no significant effect of condition on answer accuracy,  $F(2, 1167) = 2.81, P = 0.061$ , but a trend toward significance, as performances were better on ToMC than in the other two conditions (ToMA and PC). Mean reaction times were 3009 ms for ToMA (s.d. = 1226, range = 1722–7047), 2868 ms for ToMC (s.d. = 1126, range = 1604–7136) and 3010 ms for PC (s.d. = 1212, range = 1694–7849). There was no significant effect of condition on reaction times,  $F(2, 1167) = 1.85, P = 0.158$ .

## Functional fMRI results

The regions that reached cluster-level significance at  $P < 0.05$ , FWE-corrected, for the four contrasts of interest (ToMA > PC, ToMC > PC, ToMA > ToMC and ToMC > ToMA) are reported in Table 2 and illustrated in Figure 1. For the ToMA > PC contrast, clusters of significant activation were found in the mPFC, precuneus/posterior cingulate cortex (PCC), superior temporal gyrus and temporoparietal junction, MTG, anterior cingulate cortex and inferior frontal gyrus (Figure 1A). For the ToMC > PC contrast, clusters were found in the precuneus and medial occipital gyrus (Figure 1B). For the ToMA > ToMC contrast, clusters were found in the mPFC and PCC (Figure 1B), while for the ToMC > ToMA contrast, clusters were found in the bilateral lingual gyri and left fusiform gyrus.

Analyses of whole-brain activation with the total SPQ score as a covariate revealed a significant positive correlation for the ToMA > PC contrast in the posterior brain regions, mostly in the left hemisphere, as reported in Table 3 and Figure 2.

## Brain-behavior associations

Four brain regions were found to be associated with clinical scores for the ToMA > PC contrast. First, the activity of the left MTG [Brodmann area (BA): 22; MNI coordinates:  $x = -58, y = -42$  and  $z = 6$ ] was positively correlated with the total SPQ score ( $\rho = 0.487, P < 0.01$ ), positive SPQ ( $\rho = 0.445, P = 0.005$ ) and negative SPQ ( $\rho = 0.414, P < 0.01$ ). Second, the activity of the right inferior occipital gyrus (IOG; BA: 19; MNI:  $x = 46, y = -76$  and  $z = -8$ ) was negatively correlated with the BES emotional disconnection subscore ( $\rho = -0.443, P = 0.005$ ). Third, the activity in the right MTG (BA: 39; MNI:  $x = 52, y = -58$  and  $z = 10$ ) was negatively correlated with the total BES score ( $\rho = -0.346, P < 0.05$ ). Finally, a negative

correlation was found between precuneus activation (BA: 7; MNI:  $x = -2, y = -56$  and  $z = 38$ ) and the total BES score ( $\rho = -0.333, P < 0.05$ ).

For ToMA > ToMC contrast, activation in the left PCC (BA: 31; MNI:  $x = -2, y = -46$  and  $z = 30$ ) was negatively correlated with the emotional disconnection subscore of BES ( $\rho = -0.340, P < 0.05$ ).

A negative correlation was noted for the ToMC > ToMA contrast between the left lingual gyrus activation (BA: 18; MNI:  $x = -14, y = -90$  and  $z = -8$ ) and the positive SPQ ( $\rho = -0.366, P < 0.05$ ). Correlation scatter plots for SPQ scores are represented in Figure 3 and for BES scores in Figure 4.

## Discussion

In the present study, we comparatively investigated the neural bases of ToMA and ToMC in relation to trait schizotypy in a sample of nonclinical individuals. The primary goal was to show that the relationship between patterns of neural activation and trait schizotypy concerns brain structures that have previously been described as being associated with vulnerability to schizophrenia. The main finding reveals a positive correlation during ToMA processing between the total SPQ score and the brain activation in the left MTG and adjacent brain regions, namely the left lingual gyrus, fusiform gyrus and a cluster extending from the subgyral hypothalamus to the parahippocampal gyrus. Contradicting our first hypothesis, activated brain regions differed from those that are robustly reported as impaired in schizophrenia during ToM processing. One additional aim was to identify brain regions whose activation correlated with self-reported empathy and its subscores. Results suggested that the right MTG and left precuneus were negatively correlated with the total empathy score, while the left posterior cingulate and right IOG negatively correlated with the emotional disconnection subscore during ToMA processing. Therefore, the bilateral MTG seems to be involved in both trait schizotypy in the general population and emotional disconnection, the empathy component that enables emotions to be suppressed following emotional contagion while inferring the emotions of others in a social context.

As previously reported by Sebastian *et al.* (2012) in healthy adults and adolescents, the ToMA-PC contrast revealed a broader extent of brain activation that included the mPFC, a structure that has previously been reported to be critically involved in empathy and ToMA (Caillaud *et al.*, 2020). Increased activation in the posteromedial regions, including the posterior cingulate gyrus and precuneus, has consistently been reported in the literature in relation to both ToM (Schurz *et al.*, 2014) and schizotypy (Modinos *et al.*, 2010; Wang *et al.*, 2015), as well as the expression of schizophrenia-related genes (Romero-Garcia *et al.*, 2020).

The brain activation associated with the total SPQ score led to the identification of left posterior brain regions, namely the MTG, fusiform, lingual and parahippocampal gyrus, which have previously been shown to be relevant to mental imagery (Spagna *et al.*, 2021), face processing (Lobmaier *et al.*, 2008) and visuospatial cognition and memory storage (Gilbert *et al.*, 2001). Our results are in line with a number of previous studies, suggesting that abnormal left MTG functioning could serve as a marker of vulnerability to schizophrenia (Ehrlich *et al.*, 2010; Seidman *et al.*, 2014; Zhao *et al.*, 2018). Our results are also consistent with a structural MRI volumetric study in schizotypal personality disorder that found reduced cortical thickness in the left fusiform and parahippocampal gyri (Takayanagi *et al.*, 2020), providing further evidence that these regions may be associated with vulnerability to schizophrenia.

**Table 2.** Whole-brain activation

Location Areas	Hemisphere	Brodmann area	Cluster size	Significance		MNI coordinates		
				$P_{FWE-corr}$	t-values	x	y	z
ToMA > PC								
Precuneus	L	7	1372	<0.001	8.98	-2	-56	38
PCC	L	30		<0.001	7.65	-4	-48	22
Precuneus	L	7		<0.001	7.46	-6	-46	42
STJ/TPJ	R	22	644	<0.001	7.57	50	-20	-12
MTG	R	21		<0.001	7.35	52	-32	-4
MTG	R	22		<0.001	7.05	54	-38	6
mPFC	L	9	286	<0.001	7.39	-8	56	20
ACC	L	10		0.020	5.55	-2	58	2
SFG	L	9		0.046	5.22	-22	48	26
MTG	L	21	170	<0.001	7.18	-56	-10	-18
IFG orb	L	47	40	0.003	6.29	-42	30	-4
MTG	L	22	29	0.003	6.19	-58	-42	6
MTG/TPJ	L	19	251	0.004	6.18	-54	-62	18
Angular gyrus	L	39		0.005	6.06	-50	-64	38
STG	L	39		0.008	5.90	-54	-52	20
mPFC	R	9	164	0.004	6.16	2	56	18
mPFC	R	10		0.009	5.85	8	58	6
mPFC	R	10		0.024	5.47	2	56	0
IOG	R	19	25	0.009	5.84	46	-76	-8
MTG	R	37		0.025	5.46	52	-68	4
MTG	R	39	79	0.010	5.72	52	-58	10
ToMC > PC								
Precuneus	L	7	106	0.004	5.97	-6	-48	44
Precuneus	L	7		0.022	5.34	-2	-56	42
MTG/MOG	L	37	20	0.010	5.62	-50	-72	8
ToMA > ToMC								
mPFC	L	9	169	0.002	6.21	-6	54	22
PCC	L	31	106	0.003	6.18	-2	-46	30
mPFC	R	9	61	0.006	5.90	6	58	16
mPFC	R	9		0.037	5.20	2	52	26
ToMC > ToMA								
Lingual gyrus	L	18	202	<0.001	6.99	-14	-90	-8
Lingual gyrus	R	18	125	0.001	6.53	18	-86	-2
Fusiform gyrus	L	36	45	0.004	6.03	-26	-44	-12
Fusiform gyrus/ parahippocampus	R	37	25	0.016	5.53	28	-46	-10
Gyrus supramarginal	L	40	22	0.023	5.39	-58	-24	38

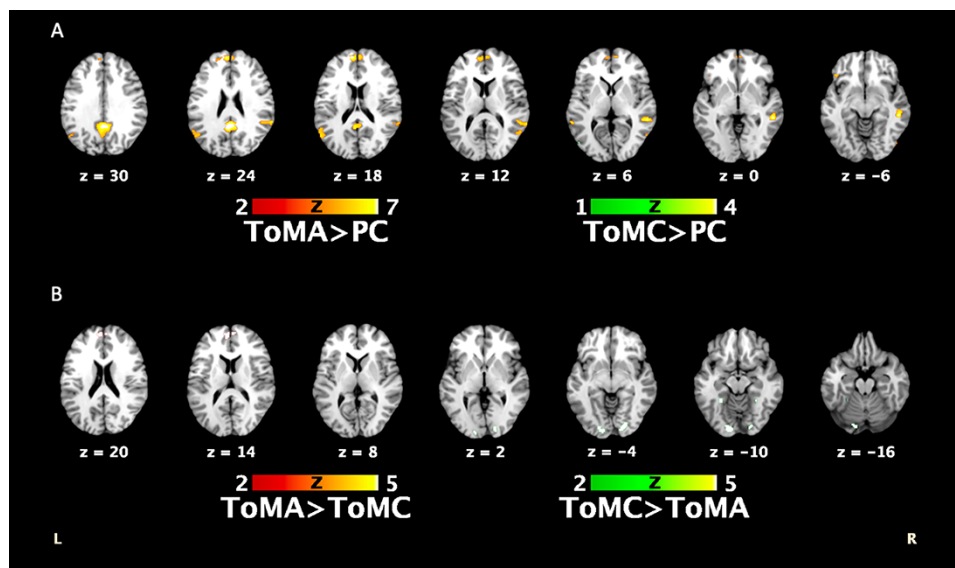
Notes. STG = superior temporal gyrus; MOG = medial occipital gyrus; ACC = anterior cingulate cortex; IFG = inferior frontal gyrus; TPJ = temporoparietal junction; L = left; R = right;  $P_{FWE-corr}$  = threshold for familywise error.  $P < 0.05$ , FWE-corrected,  $k = 20$ .

Interestingly, functional asymmetry has already been reported for face identification (Ma and Han, 2012) and language processing (Binder et al., 2011). A gradual loss of gray matter in the left MTG and its surrounding brain regions has previously been observed in adolescents with schizotypal traits and mild cognitive impairment (Moorhead et al., 2009).

To the best of our knowledge, this is the first study to suggest a specific role of the left MTG and its adjacent structures in ToMA processing in schizophrenia-related vulnerability.

Our results establish a link between ToMA processing, trait schizotypy and the activation of left posterior brain regions (MTG, lingual, fusiform and parahippocampal gyrus). Based on the literature, we suggest that there is a link with creativity as a facilitator of social adaptation. Creativity is defined as the ability to produce something new, original and appropriate to resolve a task and follows a U-shaped relation with schizophrenia spectrum disorder (Sampedro et al., 2020). Carson (2011) described a model of schizotypy where the biological factors creating vulnerability to psychopathology confer greater creative ability on individuals,

along with a higher intelligence quotient and superior metacognitive protective factors. Thus, some authors have suggested that this enhanced creativity mediates the selection of schizophrenia-related vulnerability genes through evolution (McCreery and Claridge, 2002) and explains the prevalence of trait schizotypy, evaluated at about 10% of the general population (Cohen et al., 2015). In addition, ToM and schizotypy have both been related to creativity (Suddendorf and Fletcher-Flinn, 1997). Thus, trait schizotypy may promote creative reasoning, while schizophrenia may impede it (Sampedro et al., 2020). Fisher et al. (2004) suggested that positive schizotypy is more specifically related to creative thinking, but in contrast to our findings, the authors found the underlying brain correlates in the right hemisphere, in particular the right prefrontal cortex. Divergent thinking, however, which is defined as the essence of creative thinking (Zhu et al., 2013; Zhang et al., 2016), has consistently been linked to inhibition (Benedek et al., 2012, 2014; Zhang et al., 2016). The latter is controlled by the inferior frontal gyrus (Aron et al., 2014) and promoted in secondary sensory cortices for all sensory modalities processed in



**Fig. 1.** Brain activation related to the experimental task in four contrasts of interest. (A) Main effect of ToMA and ToMC relative to PC in healthy participants. Overlapping activation was observed in the precuneus. ToMA activation was widely distributed and concerned the mPFC, precuneus/PCC, superior temporal gyrus and temporoparietal junction, MTG, anterior cingulate cortex and inferior frontal gyrus. (B) The comparison between ToMA and ToMC showed that ToMA elicited the anterior part of the mPFC and the posterior cingulate (not shown), while ToMC relied on posterior brain regions (i.e. lingual and fusiform gyri).  $P < 0.05$  FWE-corrected,  $k = 20$ .

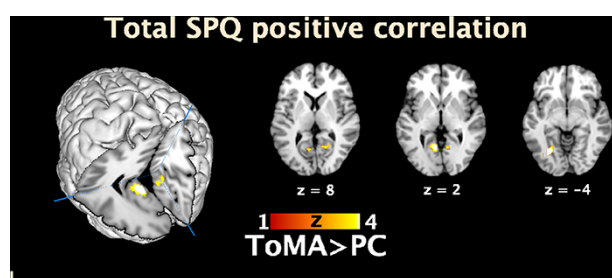
**Table 3.** Whole-brain activation with the total SPQ score as a covariate

Location	Areas	Hemisphere	Brodmann area	Cluster size	Significance		MNI coordinates		
					$P_{\text{FWE-corr}}$	t-values	x	y	z
ToMA > PC									
	Fusiform gyrus/PH	L	19	118	0.025	5.49	-30	-64	-4
	IOG	L	19		0.935	3.58	-36	-70	-6
	Calcarine gyrus/ PH	L	18	158	0.134	4.79	-8	-58	4
	Lingual gyrus	R	18	82	0.718	3.92	10	-58	4
	PCC	R	30		0.938	3.57	22	-54	8

Notes. PH = parahippocampus; PCC = posterior cingulate gyrus; L = left; R = right;  $P_{\text{FWE-corr}}$  = threshold for familywise error.  $P < 0.001$  uncorrected,  $k = 20$ .

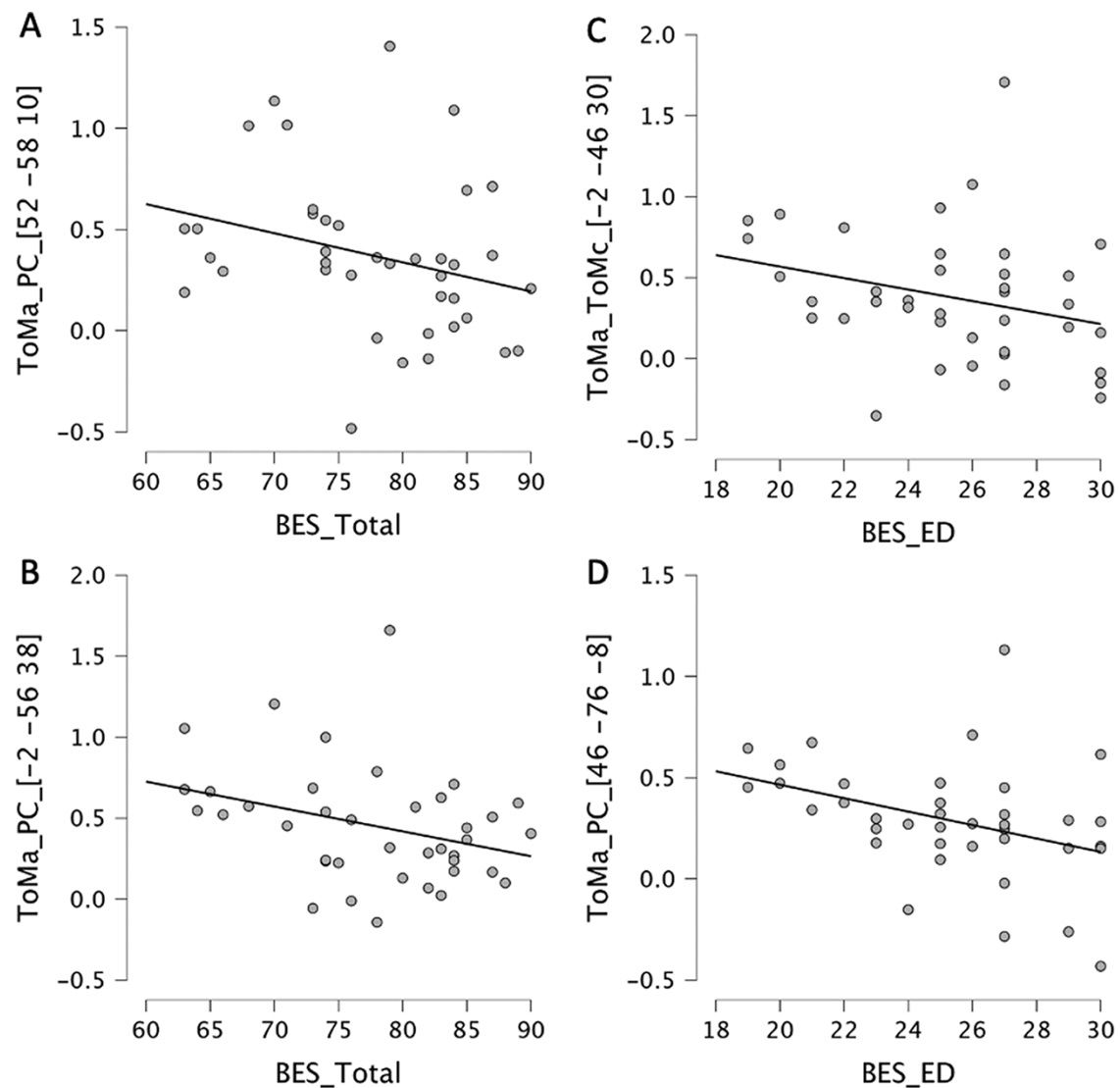
posterior brain regions surrounding the temporo-parieto-occipital junction (Zhang et al., 2016), including the MTG. In addition, hippocampal and parahippocampal regions are involved in verbal divergent thinking (Takeuchi et al., 2020). Furthermore, visual mental imagery engages the left fusiform gyrus without the early visual cortex (Spagna et al., 2021), suggesting that this region plays a fundamental role in the conception of creative ideas in individuals.

The parahippocampal gyrus has been identified as a possible multimodal association area related to schizophrenia spectrum disorders in a range of studies, including postmortem research on schizophrenia (McDonald et al., 2000) and brain tumors with secondary hallucinations (Acioly et al., 2010), and volumetric (Seidman et al., 2003; Prasad et al., 2004; Moorhead et al., 2009) and functional (Escarti et al., 2010) MRI studies. The parahippocampal gyrus is involved in high-level cognitive functioning, including memory encoding and retrieval, as well as visuospatial cognition (Lin et al., 2021). It is strongly connected to other brain regions through the inferior longitudinal fasciculus and cingulum (Lin et al., 2021), both pathways that are involved in neurodevelopmental disorders, and in particular schizophrenia (Clark et al., 2011). Consistent with our results, an asymmetry has been observed in structural MRI volumetric analysis, indicating that reduced gray matter volume in the left parahippocampal gyrus is specifically related to schizophrenia (Prasad



**Fig. 2.** The ToMA > PC contrast of brain activation when the total SPQ was modeled as a covariate revealed a positive correlation between the total SPQ and the left posterior brain regions, namely fusiform, calcarine et parahippocampal gyrus and, in lesser extent, activation was observed in the right calcarine and lingual gyrus. On the left, oblique posterior view on the 3D reconstruction.  $P < 0.001$  uncorrected,  $k = 20$ .

et al., 2004). Electrophysiological explorations using electroencephalogram (EEG) have suggested that abnormal brain activation in the left parahippocampal gyrus is specifically related to schizophrenia spectrum disorder, as it has been found in both patients with schizophrenia and their first-degree relatives, in comparison to healthy controls (Soni et al., 2020). In addition, this brain region appears to be particularly vulnerable during development and is also sensitive to environmental changes, such



**Fig. 3.** Scatter plots of significant correlations between brain activation regions for the SPQ clinical score and subscores. Brain coordinates are reported in the MNI system. In ToMA > PC contrast, we found a positive correlation between the left MTG activation and the SPQ total score (A), and positive (C) and negative (D) subscores. In ToMC > ToMA contrast, a negative correlation between the left lingual gyrus activation and the positive SPQ subscore is represented (B).

as urbanization (Besteher et al., 2017), which is thought to be the most consistent environmental risk factor for schizophrenia (van Os and Kapur, 2009).

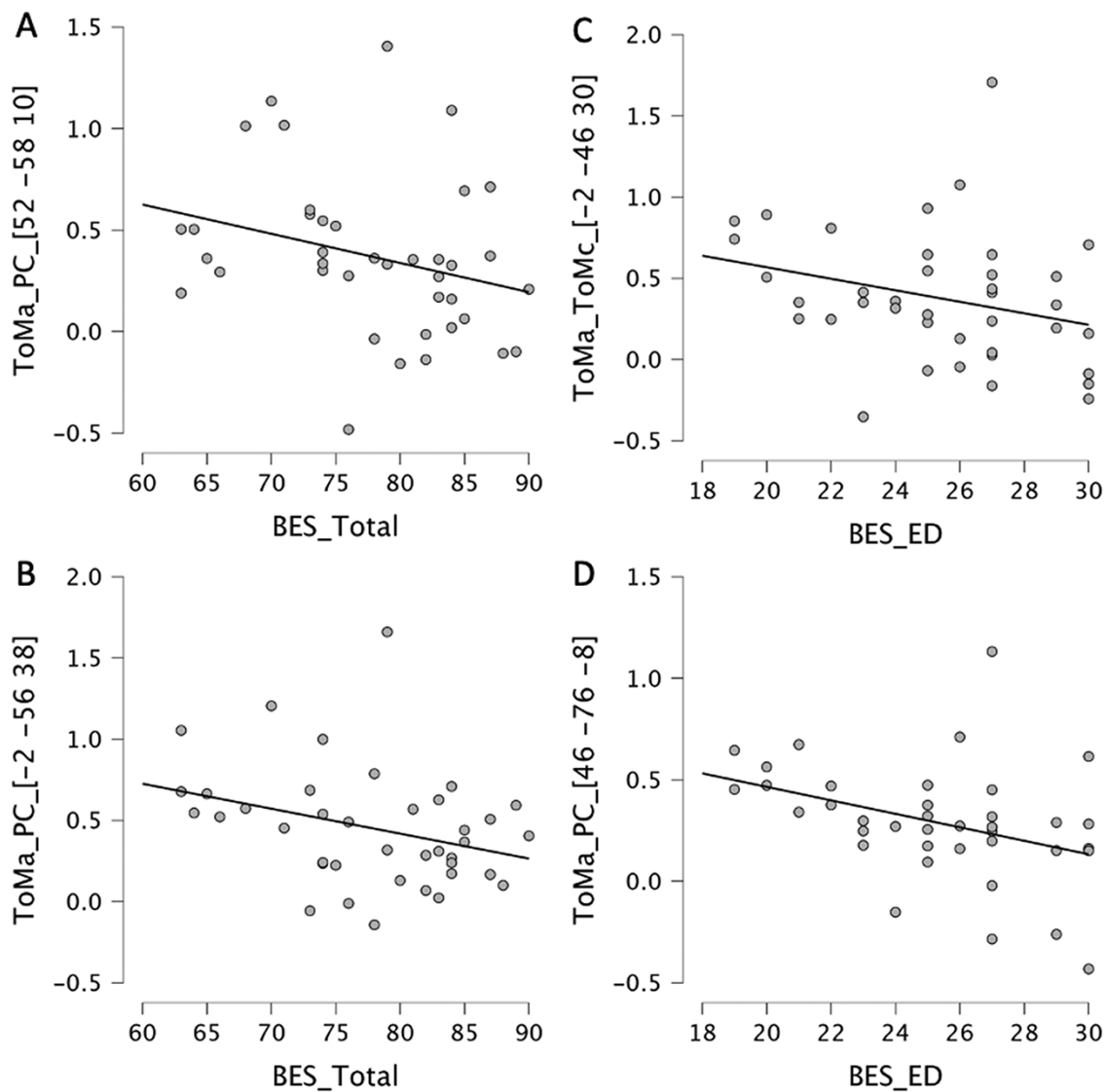
In patients with schizophrenia, the left MTG has consistently been found to be impaired at volumetric (Marsh et al., 1994), functional (Holt et al., 2006) and connectivity (Zhang et al., 2017) levels. It has also been associated with persistent auditory verbal hallucinations (Zhang et al., 2017). Importantly, reduced gray matter volume in the left MTG has been reported in first-episode and early-onset schizophrenia (Tang et al., 2012), suggesting that abnormalities in this brain region could be the most prominent marker of schizophrenia transition. Data from post-mortem studies suggest that the excitatory/inhibitory molecular balance is altered in the MTG of patients with schizophrenia, mainly as a result of changes in the expression of glutamate-signaling genes (Bobilev et al., 2020) and dopamine regulation (Allen et al., 2019) that could further lead to positive psychotic symptoms.

Our results therefore suggest that the left MTG and adjacent brain regions display impaired activation during ToMA in healthy participants with trait schizotypy and that these brain regions should be further considered in research on the developmental aspects of the transition to schizophrenia disorder.

We should acknowledge some limitations to the study. First, we included healthy individuals with a ceiling effect on the task performance. Nevertheless, we aimed to identify how brain activation during the task would correlate with SPQ scores rather than a task performance *per se*. Second, the fMRI analyses were based on a relatively small sample that limits both the robustness of our data and the statistical application of more stringent thresholds. Therefore, the generalization of our results is limited, and this would be the first encouraging step to the other studies on the subject.

In conclusion, the present study highlights the specific changes in brain activation during ToMA (but not ToMC) processing that





**Fig. 4.** Scatter plots of significant correlations between brain activation regions for the BES clinical score and subscores. Brain coordinates are reported in the MNI system. In ToMA > PC contrast, we found a positive correlation between the total BES score and the right MTG (A), and precuneus (B). Emotional disconnection clinical subscore correlated negatively to the right IOG in ToMA > PC contrast (C) and to the PCC in ToMA > ToMC contrast (D).

are associated with trait schizotypy in nonclinical individuals. These results have several implications and open up new avenues for investigating the continuum between schizotypy and schizophrenia in relation to social skill difficulties, as well as for investigating the neural brain processing related to ToM.

## Acknowledgements

We are very grateful to Catherine Sebastian, who kindly provided the cartoon task material. We would like to thank all the participants. The data that support the findings of this study are available on request from the corresponding author, K.V.

## Authors contributions

The study was originally conceived by K.V., P.G., S.C. and A.K., with D.R.C., A.H. and F.G. F.G., A.O. and C.P. contributed to the design of the imaging procedure. Inclusions were conducted by K.V., D.R.C. and M.T., who collected the data. S.B. guided

participants throughout the experimental procedure and managed the database prior to the statistical analysis. Behavioral data were analyzed by K.V., and imaging data were analyzed by A.O. F.G., S.C. and A.K. were responsible for project management and funding acquisition. All authors participated in the data interpretation. K.V. wrote the draft manuscript, and all the authors contributed to the final version of the manuscript.

## Funding

This research was funded by a grant to A.K. under the aegis of a collaborative project (PHU) between the University of Reims Champagne-Ardenne (URCA) and Reims University Hospital (CHU de Reims) on Social Cognition and Neurodevelopmental Disorders (Ndev-X).

## Conflict of interest

The authors declared that they had no conflict of interest with respect to their authorship or the publication of this article.

## References

- Acioly, M.A., Carvalho, C.H., Tatagiba, M., Gharabaghi, A. (2010). The parahippocampal gyrus as a multimodal association area in psychosis. *Journal of Clinical Neuroscience*, **17**(12), 1603–5. [10.1016/j.jocn.2010.03.052](https://doi.org/10.1016/j.jocn.2010.03.052).
- Allen, P., Moore, H., Corcoran, C.M., et al. (2019). Emerging temporal lobe dysfunction in people at clinical high risk for psychosis. *Frontiers in Psychiatry*, **10**, 298. [10.3389/fpsy.2019.00298](https://doi.org/10.3389/fpsy.2019.00298).
- American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Arlington, VA.
- Aron, A.R., Robbins, T.W., Poldrack, R.A. (2014). Inhibition and the right inferior frontal cortex: one decade on. *Trends in Cognitive Sciences*, **18**(4), 177–85. [10.1016/j.tics.2013.12.003](https://doi.org/10.1016/j.tics.2013.12.003).
- Barrantes-Vidal, N., Chun, C.A., Myin-Germeys, I., Kwapil, T.R. (2013). Psychometric schizotypy predicts psychotic-like, paranoid, and negative symptoms in daily life. *Journal of Abnormal Psychology*, **122**(4), 1077–87. [10.1037/a0034793](https://doi.org/10.1037/a0034793).
- Barrantes-Vidal, N., Sheinbaum, T., Ballespi, S., Chun, C., Myin-Germeys, I., Kwapil, T.R. (2014). Ecological validity of the schizotypy dimensions and stress-reactivity model of psychotic-like experiences. *Schizophrenia Research*, **153**(1), S267. [10.1016/S0920-9964\(14\)70762-5](https://doi.org/10.1016/S0920-9964(14)70762-5).
- Bartholomeusz, C.F., Ganella, E.P., Whittle, S., et al. (2018). An fMRI study of theory of mind in individuals with first episode psychosis. *Psychiatry Research - Neuroimaging*, **281**(March), 1–11. [10.1016/j.pscychresns.2018.08.011](https://doi.org/10.1016/j.pscychresns.2018.08.011).
- Benedek, M., Franz, F., Heene, M., Neubauer, A.C. (2012). Differential effects of cognitive inhibition and intelligence on creativity. *Personality and Individual Differences*, **53–334**(4), 480–5. [10.1016/j.paid.2012.04.014](https://doi.org/10.1016/j.paid.2012.04.014).
- Benedek, M., Jauk, E., Sommer, M., Arendasy, M., Neubauer, A.C. (2014). Intelligence, creativity, and cognitive control: the common and differential involvement of executive functions in intelligence and creativity. *Intelligence*, **46**, 73–83. [10.1016/j.intell.2014.05.007](https://doi.org/10.1016/j.intell.2014.05.007).
- Bensalah, L., Caillies, S., Anduze, M. (2016). Links among cognitive empathy, theory of mind, and affective perspective taking by young children. *Journal of Genetic Psychology*, **177**(1), 17–31. [10.1080/00221325.2015.1106438](https://doi.org/10.1080/00221325.2015.1106438).
- Besteher, B., Gaser, C., Spalthoff, R., Nenadić, I. (2017). Associations between urban upbringing and cortical thickness and gyrification. *Journal of Psychiatric Research*, **95**, 114–20. [10.1016/j.jpsy.2017.08.012](https://doi.org/10.1016/j.jpsy.2017.08.012).
- Binder, J.R., Gross, W.L., Allendorfer, J.B., et al. (2011). Mapping anterior temporal lobe language areas with fMRI: a multicenter normative study. *NeuroImage*, **54**(2), 1465–75. [10.1016/j.neuroimage.2010.09.048](https://doi.org/10.1016/j.neuroimage.2010.09.048).
- Bitsch, F., Berger, P., Nagels, A., Falkenberg, I., Straube, B. (2021). Characterizing the theory of mind network in schizophrenia reveals a sparser network structure. *Schizophrenia Research*, **228**, 581–9. [10.1016/j.schres.2020.11.026](https://doi.org/10.1016/j.schres.2020.11.026).
- Bobilev, A.M., Perez, J.M., Tamminga, C.A. (2020). Molecular alterations in the medial temporal lobe in schizophrenia. *Schizophrenia Research*, **217**, 71–85. [10.1016/j.schres.2019.06.001](https://doi.org/10.1016/j.schres.2019.06.001).
- Bodden, M.E., Kübler, D., Knake, S., et al. (2013). Comparing the neural correlates of affective and cognitive theory of mind using fMRI: involvement of the basal ganglia in affective theory of mind. *Advances in Cognitive Psychology*, **9**(1), 32–43. [10.2478/v10053-008-0129-6](https://doi.org/10.2478/v10053-008-0129-6).
- Bohec, A.L., Baltazar, M., Tassin, M., Rey, R. (2021). Theory of mind and schizotypy: a review. *Encephale*, **47**(3), 254–62. [10.1016/j.encep.2020.10.007](https://doi.org/10.1016/j.encep.2020.10.007).
- Bora, E. (2020). Theory of mind and schizotypy: a meta-analysis. *Schizophrenia Research*, **222**, 97–103. [10.1016/j.schres.2020.04.024](https://doi.org/10.1016/j.schres.2020.04.024).
- Bora, E., Baysan Arabaci, L. (2009). Effect of age and gender on schizotypal personality traits in the normal population. *Psychiatry and Clinical Neurosciences*, **63**(5), 663–9. [10.1111/j.1440-1819.2009.02011.x](https://doi.org/10.1111/j.1440-1819.2009.02011.x).
- Burns, J.K. (2006). Psychosis: a costly by-product of social brain evolution in *Homo sapiens*. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, **30**(5), 797–814. [10.1016/j.pnpb.2006.01.006](https://doi.org/10.1016/j.pnpb.2006.01.006).
- Caillaud, M., Bejanin, A., Laisney, M., et al. (2020). Influence of emotional complexity on the neural substrates of affective theory of mind. *Human Brain Mapping*, **41**(1), 139–49. [10.1002/hbm.24794](https://doi.org/10.1002/hbm.24794).
- Carré, A., Stefaniak, N., D'Ambrosio, F., Bensalah, L., Besche-Richard, C. (2013). The basic empathy scale in adults (BES-A): factor structure of a revised form. *Psychological Assessment*, **25**(3), 679. [10.1037/a0032297](https://doi.org/10.1037/a0032297).
- Carson, S.H. (2011). Creativity and psychopathology: a shared vulnerability model. *Canadian Journal of Psychiatry*, **56**(3), 144–53. [10.1177/070674371105600304](https://doi.org/10.1177/070674371105600304).
- Catts, V.S., Fung, S.J., Long, L.E., et al. (2013). Rethinking schizophrenia in the context of normal neurodevelopment. *Frontiers in Cellular Neuroscience*, **7**, 60. [10.3389/fncel.2013.00060](https://doi.org/10.3389/fncel.2013.00060).
- Chmielewski, M., Watson, D. (2008). The heterogeneous structure of schizotypal personality disorder: item-level factors of the Schizotypal Personality Questionnaire and their associations with obsessive-compulsive disorder symptoms, dissociative tendencies, and normal personality. *Journal of Abnormal Psychology*, **117**(2), 364–76. [10.1037/0021-843X.117.2.364](https://doi.org/10.1037/0021-843X.117.2.364).
- Clark, K.A., Nuechterlein, K.H., Asarnow, R.F., et al. (2011). Mean diffusivity and fractional anisotropy as indicators of disease and genetic liability to schizophrenia. *Journal of Psychiatric Research*, **45**(7), 980–8. [10.1016/j.jpsy.2011.01.006](https://doi.org/10.1016/j.jpsy.2011.01.006).
- Cohen, A.S., Mohr, C., Ettinger, U., Chan, R.C.K., Park, S. (2015). Schizotypy as an organizing framework for social and affective sciences. *Schizophrenia Bulletin*, **41**(Suppl 2), S427–35. [10.1093/schbul/sbu195](https://doi.org/10.1093/schbul/sbu195).
- Compton, M.T., Goulding, S.M., Bakeman, R., McClure-Tone, E.B. (2009). Confirmation of a four-factor structure of the Schizotypal Personality Questionnaire among undergraduate students. *Schizophrenia Research*, **111**(1–3), 46–52. [10.1016/j.schres.2009.02.012](https://doi.org/10.1016/j.schres.2009.02.012).
- Dennis, M., Simic, N., Bigler, E.D., et al. (2013). Cognitive, affective, and conative theory of mind (ToM) in children with traumatic brain injury. *Developmental Cognitive Neuroscience*, **525–39**. [10.1016/j.dcn.2012.11.006](https://doi.org/10.1016/j.dcn.2012.11.006).
- Dodell-Feder, D., Tully, L.M., Lincoln, S.H., Hooker, C.I. (2014). The neural basis of theory of mind and its relationship to social functioning and social anhedonia in individuals with schizophrenia. *NeuroImage: Clinical*, **4**(November), 154–63. [10.1016/j.nicl.2013.11.006](https://doi.org/10.1016/j.nicl.2013.11.006).
- Dumas, P., Bouafia, S., Gutknecht, C., Saoud, M., Dalery, J., d'Amato, T. (2000). Validation of the French version of the Raine Schizotypal Personality Disorder Questionnaire—categorical and dimensional approach to schizotypal personality traits in a normal student population. *Encéphale*, **26**(5), 23–9.
- Ehrlich, S., Morrow, E.M., Roffman, J.L., et al. (2010). The COMT Val108/158Met polymorphism and medial temporal lobe volume in patients with schizophrenia and healthy adults. *NeuroImage*, **53**(3), 992–1000. [10.1016/j.neuroimage.2009.12.046](https://doi.org/10.1016/j.neuroimage.2009.12.046).
- Escartí, M.J., de la Iglesia-vayá, M., Martí-Bonmatí, L., et al. (2010). Increased amygdala and parahippocampal gyrus activation in schizophrenic patients with auditory hallucinations: an

- fMRI study using independent component analysis. *Schizophrenia Research*, **117**(1), 31–41. [10.1016/j.schres.2009.12.028](https://doi.org/10.1016/j.schres.2009.12.028).
- Ettinger, U., Meyhöfer, I., Steffens, M., Wagner, M., Koutsouleris, N. (2014). Genetics, cognition, and neurobiology of schizotypal personality: a review of the overlap with schizophrenia. *Frontiers in Psychiatry*, **5**, 18. [10.3389/fpsy.2014.00018](https://doi.org/10.3389/fpsy.2014.00018).
- Fink, A., Weber, B., Koschutnig, K., Benedek, M., Reishofer, G., Ebner, F., et al. (2014). Creativity and schizotypy from the neuroscience perspective. *Cognitive, Affective and Behavioral Neuroscience*, **14**(1). [10.3758/s13415-013-0210-6](https://doi.org/10.3758/s13415-013-0210-6).
- Fisher, J.E., Mohanty, A., Herrington, J.D., Koven, N.S., Miller, G.A., Heller, W. (2004). Neuropsychological evidence for dimensional schizotypy: implications for creativity and psychopathology. *Journal of Research in Personality*, **17**(12), 1603–5. [10.1016/j.jrp.2003.09.014](https://doi.org/10.1016/j.jrp.2003.09.014).
- Gilbert, C.D., Sigman, M., Crist, R.E. (2001). The neural basis of perceptual learning. *Neuron*, **17**(12), 1603–5. [10.1016/S0896-6273\(01\)00424-X](https://doi.org/10.1016/S0896-6273(01)00424-X).
- Gottesman, I.I., Gould, T.D. (2003). The endophenotype concept in psychiatry: etymology and strategic intentions. *American Journal of Psychiatry*, **160**(4), 636–45. [10.1176/appi.ajp.160.4.636](https://doi.org/10.1176/appi.ajp.160.4.636).
- Goulding, A. (2004). Schizotypy models in relation to subjective health and paranormal beliefs and experiences. *Personality and Individual Differences*, **37**(1), 157–67. [10.1016/j.paid.2003.08.008](https://doi.org/10.1016/j.paid.2003.08.008).
- Guloksuz, S., Van Os, J. (2018). The slow death of the concept of schizophrenia and the painful birth of the psychosis spectrum. *Psychological Medicine*, **48**(2), 229–44. [10.1017/S0033291717001775](https://doi.org/10.1017/S0033291717001775).
- Holt, D.J., Kunkel, L., Weiss, A.P., et al. (2006). Increased medial temporal lobe activation during the passive viewing of emotional and neutral facial expressions in schizophrenia. *Schizophrenia Research*, **82**(2–3), 153–62. [10.1016/j.schres.2005.09.021](https://doi.org/10.1016/j.schres.2005.09.021).
- Jacquet, J., Delpech, L., Bronchain, J., Raynal, P. (2020). Creative competencies and cognitive processes associated with creativity are linked with positive schizotypy. *Creativity Research Journal*, **32**(2), 142–50. [10.1080/10400419.2020.1733895](https://doi.org/10.1080/10400419.2020.1733895).
- Jáni, M., Kašpárek, T. (2018). Emotion recognition and theory of mind in schizophrenia: a meta-analysis of neuroimaging studies. *World Journal of Biological Psychiatry*, **19**(Sup3), S86–96. [10.1080/15622975.2017.1324176](https://doi.org/10.1080/15622975.2017.1324176).
- Kahn, R.S., Sommer, I.E. Murray, R.M., et al. (2015). Schizophrenia. *Nature Reviews Disease Primers*. [10.1038/nrdp.2015.67](https://doi.org/10.1038/nrdp.2015.67).
- Kocsis-Bogár, K., Kotulla, S., Maier, S., Voracek, M., Hennig-Fast, K. (2017). Cognitive correlates of different mentalizing abilities in individuals with high and low trait schizotypy: findings from an extreme-group design. *Frontiers in Psychology*, **8**(Jun). [10.3389/fpsyg.2017.00922](https://doi.org/10.3389/fpsyg.2017.00922).
- Kronbichler, L., Tschernegg, M., Martin, A.I., Schurz, M., Kronbichler, M. (2017). Abnormal brain activation during theory of mind tasks in schizophrenia: a meta-analysis. *Schizophrenia Bulletin*, **43**(6), 1240–50. [10.1093/schbul/sbx073](https://doi.org/10.1093/schbul/sbx073).
- Lech, R.K., Güntürkün, O., Suchan, B. (2016). An interplay of fusiform gyrus and hippocampus enables prototype- and exemplar-based category learning. *Behavioural Brain Research*, **311**, 239–46. [10.1016/j.bbr.2016.05.049](https://doi.org/10.1016/j.bbr.2016.05.049).
- Leung, C., Lei, K.S., Wang, S.M., Lam, B.Y.H. (2021). Theory of mind in schizotypy: a behavioral and event-related potential (ERP) study. *Schizophrenia Research: Cognition*, **23**, 100190. [10.1016/j.scog.2020.100190](https://doi.org/10.1016/j.scog.2020.100190).
- Lin, Y.H., Dhanaraj, V., Mackenzie, A.E., et al. (2021). Anatomy and white matter connections of the parahippocampal gyrus. *World Neurosurgery*, **148**, e218–26. [10.1016/j.wneu.2020.12.136](https://doi.org/10.1016/j.wneu.2020.12.136).
- Lobmaier, J.S., Klaver, P., Loenneker, T., Martin, E., Mast, F.W. (2008). Featural and configural face processing strategies: evidence from a functional magnetic resonance imaging study. *NeuroReport*, **19**(3), 287–91. [10.1097/WNR.0b013e3282f556fe](https://doi.org/10.1097/WNR.0b013e3282f556fe).
- Ma, Y., Han, S. (2012). Functional dissociation of the left and right fusiform gyrus in self-face recognition. *Human Brain Mapping*, **33**, 2255–67. [10.1002/hbm.21356](https://doi.org/10.1002/hbm.21356).
- Marsh, L., Suddath, R.L., Higgins, N., Weinberger, D.R. (1994). Medial temporal lobe structures in schizophrenia: relationship of size to duration of illness. *Schizophrenia Research*, **11**(3), 225–38. [10.1016/0920-9964\(94\)90016-7](https://doi.org/10.1016/0920-9964(94)90016-7).
- Martin, A.K., Robinson, G., Dzaifc, I., Reutens, D., Mowry, B. (2014). Theory of mind and the social brain: implications for understanding the genetic basis of schizophrenia. *Genes, Brain, and Behavior*, **13**(1), 104–17. [10.1111/gbb.12066](https://doi.org/10.1111/gbb.12066).
- McCreery, C., Claridge, G. (2002). Healthy schizotypy: the case of out-of-the-body experiences. *Personality and Individual Differences*, **32**(1), 141–54. [10.1016/S0191-8869\(01\)00013-7](https://doi.org/10.1016/S0191-8869(01)00013-7).
- McDonald, B., Highley, J.R., Walker, M.A., et al. (2000). Anomalous asymmetry of fusiform and parahippocampal gyrus gray matter in schizophrenia: a postmortem study. *American Journal of Psychiatry*, **157**(1), 40–7. [10.1176/ajp.157.1.40](https://doi.org/10.1176/ajp.157.1.40).
- McDonald, H., Babunashvili, M., Finn, A., et al. (2021). Positive schizotypy and the experience of creativity: the distinctive roles of suspiciousness and dispositional mindfulness. *Schizophrenia Research*, **228**, 151–58. [10.1016/j.schres.2020.12.004](https://doi.org/10.1016/j.schres.2020.12.004).
- Modenato, C., Draganski, B. (2015). The concept of schizotypy—a computational anatomy perspective. *Schizophrenia Research: Cognition*, **2**(2), 89–2. [10.1016/j.scog.2015.05.001](https://doi.org/10.1016/j.scog.2015.05.001).
- Modinos, G., Mechelli, A., Ormel, J., Groenewold, N.A., Aleman, A., McGuire, P.K. (2010). Schizotypy and brain structure: a voxel-based morphometry study. *Psychological Medicine*, **40**(9), 1423–31. [10.1017/S0033291709991875](https://doi.org/10.1017/S0033291709991875).
- Mohnke, S., Erk, S., Schnell, K., et al. (2014). Further evidence for the impact of a genome-wide-supported psychosis risk variant in ZNF804A on the theory of mind network. *Neuropsychopharmacology*, **39**(5), 1196–205. [10.1038/npp.2013.321](https://doi.org/10.1038/npp.2013.321).
- Moorhead, T.W.J., Stanfield, A., Spencer, M., et al. (2009). Progressive temporal lobe grey matter loss in adolescents with schizotypal traits and mild intellectual impairment. *Psychiatry Research – Neuroimaging*, **174**(2), 105–9. [10.1016/j.psychres.2009.04.003](https://doi.org/10.1016/j.psychres.2009.04.003).
- Morton, S.E., O'Hare, K.J.M., Maha, J.L.K., et al. (2017). Testing the validity of taxonic schizotypy using genetic and environmental risk variables. *Schizophrenia Bulletin*, **43**(3), 633–43. [10.1093/schbul/sbw108](https://doi.org/10.1093/schbul/sbw108).
- Narme, P., Mouras, H., Loas, G., et al. (2010). Vers une approche neuropsychologique de l'empathie. *Revue de Neuropsychologie*, **2**(4), 292–98. [10.3917/rne.024.0292](https://doi.org/10.3917/rne.024.0292).
- Nelson, B., Rawlings, D. (2010). Relating schizotypy and personality to the phenomenology of creativity. *Schizophrenia Bulletin*, **36**(2), 388–99. [10.1093/schbul/sbn098](https://doi.org/10.1093/schbul/sbn098).
- Nelson, M.T., Seal, M.L., Pantelis, C., Phillips, L.J. (2013). Evidence of a dimensional relationship between schizotypy and schizophrenia: a systematic review. *Neuroscience and Biobehavioral Reviews*, **37**(3), 317–27. [10.1016/j.neubiorev.2013.01.004](https://doi.org/10.1016/j.neubiorev.2013.01.004).
- Park, H.R.P., Kirk, I.J., Waldie, K.E. (2015). Neural correlates of creative thinking and schizotypy. *Neuropsychologia*, **73**, 94–107. [10.1016/j.neuropsychologia.2015.05.007](https://doi.org/10.1016/j.neuropsychologia.2015.05.007).
- Pinkham, A.E., Penn, D.L., Green, M.F., Buck, B., Healey, K., Harvey, P.D. (2014). The social cognition psychometric evaluation study: results of the expert survey and RAND panel. *Schizophrenia Bulletin*, **40**(4), 813–23. [10.1093/schbul/sbt081](https://doi.org/10.1093/schbul/sbt081).
- Prasad, K.M.R., Rohm, B.R., Keshavan, M.S. (2004). Parahippocampal gyrus in first episode psychotic disorders: a structural magnetic

- resonance imaging study. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, **28**(4), 651–58. [10.1016/j.pnpbp.2004.01.017](https://doi.org/10.1016/j.pnpbp.2004.01.017).
- Raine, A. (1991). The SPQ: a scale for the assessment of schizotypal personality based on DSM-III-R criteria. *Schizophrenia Bulletin*, **17**(4), 555–64. [10.1093/schbul/17.4.555](https://doi.org/10.1093/schbul/17.4.555).
- Raine, A., Reynolds, C., Lencz, T., Scerbo, A., Triphon, N., Kim, D. (1994). Cognitive-perceptual, interpersonal, and disorganized features of schizotypal personality. *Schizophrenia Bulletin*, **20**(1), 191–1. [10.1093/schbul/20.1.191](https://doi.org/10.1093/schbul/20.1.191).
- Raucher-Chéné, D., Lavigne, K.M., Makowski, C., Lepage, M. (2020). Altered surface area covariance in the mentalizing network in schizophrenia: insight into theory of mind processing. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, **17**(12), 1603–5. [10.1016/j.bpsc.2020.06.020](https://doi.org/10.1016/j.bpsc.2020.06.020).
- Rolls, E.T., Joliot, M., Tzourio-Mazoyer, N. (2015). Implementation of a new parcellation of the orbitofrontal cortex in the automated anatomical labeling atlas. *NeuroImage*, **122**, 1–5. [10.1016/j.neuroimage.2015.07.075](https://doi.org/10.1016/j.neuroimage.2015.07.075).
- Romero-Garcia, R., Seidlitz, J., Whitaker, K.J., et al. (2020). Schizotypy-related magnetization of cortex in healthy adolescence is collocated with expression of schizophrenia-related genes. *Biological Psychiatry*, **88**(3), 248–59. [10.1016/j.biopsych.2019.12.005](https://doi.org/10.1016/j.biopsych.2019.12.005).
- Sampedro, A., Peña, J., Ibarretxe-Bilbao, N., et al. (2020). Mediating role of cognition and social cognition on creativity among patients with schizophrenia and healthy controls: revisiting the shared vulnerability model. *Psychiatry and Clinical Neurosciences*, **74**(2), 149–55. [10.1111/pcn.12954](https://doi.org/10.1111/pcn.12954).
- Schlaffke, L., Lissek, S., Lenz, M., et al. (2015). Shared and nonshared neural networks of cognitive and affective theory-of-mind: a neuroimaging study using cartoon picture stories. *Human Brain Mapping*, **36**(1), 29–39. [10.1002/hbm.22610](https://doi.org/10.1002/hbm.22610).
- Schurz, M., Radua, J., Aichhorn, M., Richlan, F., Perner, J. (2014). Fractionating theory of mind: a meta-analysis of functional brain imaging studies. *Neuroscience and Biobehavioral Reviews*, **42**, 9–34. [10.1016/j.neubiorev.2014.01.009](https://doi.org/10.1016/j.neubiorev.2014.01.009).
- Sebastian, C.L., Fontaine, N.M.G., Bird, G., et al. (2012). Neural processing associated with cognitive and affective theory of mind in adolescents and adults. *Social Cognitive and Affective Neuroscience*, **7**(1), 53–63. [10.1093/scan/nsr023](https://doi.org/10.1093/scan/nsr023).
- Seidman, L.J., Pantelis, C., Keshavan, M.S., et al. (2003). A review and new report of medial temporal lobe dysfunction as a vulnerability indicator for schizophrenia: a magnetic resonance imaging morphometric family study of the parahippocampal gyrus. *Schizophrenia Bulletin*, **29**(4), 803–30. [10.1093/oxfordjournals.schbul.a007048](https://doi.org/10.1093/oxfordjournals.schbul.a007048).
- Seidman, L.J., Rosso, I.M., Thermenos, H.W., et al. (2014). Medial temporal lobe default mode functioning and hippocampal structure as vulnerability indicators for schizophrenia: a MRI study of non-psychotic adolescent first-degree relatives. *Schizophrenia Research*, **159**(2–3), 426–34. [10.1016/j.schres.2014.09.011](https://doi.org/10.1016/j.schres.2014.09.011).
- Sheehan, D.V., Lecrubier, Y., Sheehan, K.H., et al. (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *Journal of Clinical Psychiatry*, **59**.
- Soni, S., Muthukrishnan, S.P., Sood, M., Kaur, S., Sharma, R. (2020). Altered parahippocampal gyrus activation and its connectivity with resting-state network areas in schizophrenia: an EEG study. *Schizophrenia Research*, **222**, 411–22. [10.1016/j.schres.2020.03.066](https://doi.org/10.1016/j.schres.2020.03.066).
- Spagna, A., Hajhajate, D., Liu, J., Bartolomeo, P. (2021). Visual mental imagery engages the left fusiform gyrus, but not the early visual cortex: a meta-analysis of neuroimaging evidence. *Neuroscience and Biobehavioral Reviews*, **122**, 201–17. [10.1016/j.neubiorev.2020.12.029](https://doi.org/10.1016/j.neubiorev.2020.12.029).
- Stefanis, N.C., Smyrnis, N., Avramopoulos, D., Evdokimidis, I., Ntzoufras, I., Stefanis, C.N. (2004). Factorial composition of self-rated schizotypal traits among young males undergoing military training. *Schizophrenia Bulletin*, **30**, 335–50. [10.1093/oxfordjournals.schbul.a007083](https://doi.org/10.1093/oxfordjournals.schbul.a007083).
- Suddendorf, T., Fletcher-Flinn, C.M. (1997). Theory of mind and the origin of divergent thinking. *Journal of Creative Behavior*, **31**(3), 169–79. [10.1002/j.2162-6057.1997.tb00789.x](https://doi.org/10.1002/j.2162-6057.1997.tb00789.x).
- Takayanagi, Y., Sasabayashi, D., Takahashi, T., et al. (2020). Reduced cortical thickness in schizophrenia and schizotypal disorder. *Schizophrenia Bulletin*, **46**(2), 387–94. [10.1093/schbul/sbz051](https://doi.org/10.1093/schbul/sbz051).
- Takeuchi, H., Taki, Y., Nouchi, R., et al. (2020). Originality of divergent thinking is associated with working memory-related brain activity: evidence from a large sample study: originality and brain activity. *NeuroImage*, **216**, 116825. [10.1016/j.neuroimage.2020.116825](https://doi.org/10.1016/j.neuroimage.2020.116825).
- Tang, J., Liao, Y., Zhou, B., et al. (2012). Decrease in temporal gyrus gray matter volume in first-episode, early onset schizophrenia: an MRI study. *PLOS ONE*. [10.1371/journal.pone.0040247](https://doi.org/10.1371/journal.pone.0040247).
- van Os, J., Kapur, S. (2009). Schizophrenia. *The Lancet*. [10.1016/S0140-6736\(09](https://doi.org/10.1016/S0140-6736(09).
- Vucurovic, K., Caillies, S., Kaladjian, A. (2020). Neural correlates of theory of mind and empathy in schizophrenia: an activation likelihood estimation meta-analysis. *Journal of Psychiatric Research*, **120**, 163–74. [10.1016/j.jpsychires.2019.10.018](https://doi.org/10.1016/j.jpsychires.2019.10.018).
- Vucurovic, K., Caillies, S., Kaladjian, A. (2021). Neural correlates of mentalizing in individuals with clinical high risk for schizophrenia: ALE meta-analysis. *Frontiers in Psychiatry*, **12**. [10.3389/fpsy.2021.634015](https://doi.org/10.3389/fpsy.2021.634015).
- Wang, Y., Liu, W.H., Li, Z., et al. (2015). Dimensional schizotypy and social cognition: an fMRI imaging study. *Frontiers in Behavioral Neuroscience*, **9**, 1–9. [10.3389/fnbeh.2015.00133](https://doi.org/10.3389/fnbeh.2015.00133).
- Wellman, H.M., Liu, D. (2004). Scaling of theory-of-mind tasks. *Child Development*, **75**(2), 523–41. [10.1111/j.1467-8624.2004.00691.x](https://doi.org/10.1111/j.1467-8624.2004.00691.x).
- Wuthrich, V.M., Bates, T.C. (2006). Confirmatory factor analysis of the three-factor structure of the Schizotypal Personality Questionnaire and Chapman schizotypy scales. *Journal of Personality Assessment*, **87**(3), 292–4. [10.1207/s15327752jpa8703\\_10](https://doi.org/10.1207/s15327752jpa8703_10).
- Zhang, L., Qiao, L., Chen, Q., et al. (2016). Gray matter volume of the lingual gyrus mediates the relationship between inhibition function and divergent thinking. *Frontiers in Psychology*. [10.3389/fpsyg.2016.01532](https://doi.org/10.3389/fpsyg.2016.01532).
- Zhang, L., Li, B., Wang, H., et al. (2017). Decreased middle temporal gyrus connectivity in the language network in schizophrenia patients with auditory verbal hallucinations. *Neuroscience Letters*, **653**, 177–82. [10.1016/j.neulet.2017.05.042](https://doi.org/10.1016/j.neulet.2017.05.042).
- Zhao, C., Zhu, J., Liu, X., et al. (2018). Structural and functional brain abnormalities in schizophrenia: a cross-sectional study at different stages of the disease. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, **83**, 27–2. [10.1016/j.pnpbp.2017.12.017](https://doi.org/10.1016/j.pnpbp.2017.12.017).
- Zhu, F., Zhang, Q., Qiu, J. (2013). Relating inter-individual differences in verbal creative thinking to cerebral structures: an optimal voxel-based morphometry study. *PLOS ONE*. [10.1371/journal.pone.0079272](https://doi.org/10.1371/journal.pone.0079272).