



The relationship between the default mode network and the theory of mind network as revealed by psychedelics – A meta-analysis

Carla Soares¹, Gerardo Gonzalo¹, João Castelhana, Miguel Castelo-Branco^{*}

CIBIT/ ICNAS, Faculty of Medicine, University of Coimbra, R. Santa Comba, 3000-548 Coimbra, Portugal

ARTICLE INFO

Keywords:

Default mode network
Theory of mind
Psychedelics
Meta-analysis

ABSTRACT

The Default Mode Network (DMN) and the Theory of Mind (ToM) networks play a crucial role in our understanding of the neurocognition of the self. The DMN is commonly associated with introspection, while the ToM is involved in perspective-taking. There is no research investigating the overlap between the DMN and ToM in relation to causal effects such as induced by psychedelics, and their precise relationship remains therefore unknown. Psychedelics alter self-perception and modulate these networks, providing a unique opportunity to shed light on this relationship. We performed a quantitative meta-analysis of 88 studies with a total of 2122 participants to investigate the overlap between DMN and ToM and whether psychedelics affect their neural relationship. We found that the cingulate cortex (BA23 and BA31) plays a crucial role in the overlap between these networks which is substantiated by the effects of psychedelics. These compounds affect the neural basis of ToM and social cognition, which may underlie their therapeutic potential and deepen our understanding of the neural correlates of the self.

1. Introduction

As social species, human survival heavily relies on social interactions, leading to the characterization of our species as “ultra-social animals” (Tomasello, 2014). The psychological processes that allow us to handle all these interactions receive the term social cognition. Social cognition refers to the mental operations involved in the perception, interpretation, and generation of responses to the intentions, dispositions, and behaviors of others. It includes socio-cognitive abilities that allow recognizing, manipulating, and behaving concerning socially relevant information such as face processing, facial expression processing, joint attention, theory of mind (ToM), empathy, and moral processing. These abilities require a complex neural system involving cortical and subcortical regions and their connections (Adolphs, 2001; Cotter et al., 2018). Although the “social brain” network varies depending on task demands, it is thought to include limbic regions (such as the amygdala), the prefrontal cortex, the temporoparietal junction, the anterior cingulate, and the insular cortex (Cotter et al., 2018).

Among such processes, a crucial component for navigating social contexts is ToM, defined as the cognitive operations implicated in attributing affective and cognitive mental states to ourselves and to

others, meaning feelings, beliefs, intentions, or desires (Byom and Mutlu, 2013; Frith and Frith, 2006; Molenberghs et al., 2016; Schurz et al., 2014). Through ToM, we attribute mental states to others, distinguishing them from our own. This ability is believed to be functionally coordinated by a network of brain regions including the medial prefrontal cortex (mPFC), parts of the precuneus (PreC) and posterior cingulate cortex (PCC), the temporoparietal junction (TPJ) and the posterior superior temporal sulcus (pSTS) bilaterally (Schurz et al., 2014). Overlapping brain activation between different tasks and stimuli that require thinking about the mental states of others was found in the mPFC and in the bilateral posterior TPJ, which suggests the idea of a core network for ToM (Schurz et al., 2014).

Some authors have also suggested the role of ToM in the representation of the “self”, as its responsible for the ability of perspective-taking, self-projection, and autobiographical memories (Buckner and Carroll, 2007; Corcoran and Frith, 2003; Decety and Sommerville, 2003; Happé, 2003). This presumption is supported by its anatomical overlap with the Default Mode Network (DMN), a network involved in self-related cognitive functions like rumination, introspection, self-reflective thoughts, and autobiographical memory, which can impact social cognition or operate independently (Buckner and Carroll, 2007; Meyer,

^{*} Corresponding author.

E-mail address: mcbanco@fmed.uc.pt (M. Castelo-Branco).

¹ equal contribution

Table 1

Search and matching criteria used in our meta-analysis conducted on the BrainMap Sleuth 3.0.4 database. The BrainMap Sleuth is a repository of functional and structural neuroimaging data with coordinate-based results, encompassing thousands of studies involving brain activity across a wide range of tasks and conditions. The search criteria describe the keywords used to search for relevant studies, while the matching criteria report the total number of activation foci, studies, and participants included in each group.

Dimension	Search Criteria	Matching Criteria
Social Cognition	<i>Experiments: Behavioural Domain is Cognition: Social Cognition</i>	865 activation foci
	<i>AND Subjects: Diagnosis is Normals (Mars et al., 2012)</i>	32 studies 791 participants
Theory of Mind	<i>Experiments: Paradigm Class is Theory of Mind Task</i>	675 activation foci
	<i>AND Subjects: Diagnosis is Normals (Mars et al., 2012)</i>	23 studies 526 participants
Rest / DMN	<i>Experiments: Deactivations AND Experiments: Control is Low-Level AND Experiments: Context is Normal Mapping</i>	249 activation foci
	<i>(Laird et al., 2009)</i>	16 studies 482 participants

2019; Schilbach et al., 2008). The DMN was first defined as those regions of the brain which activity increased during resting-state while showing decreased activity during outward-attention-related tasks (Raichle, 2011). These brain regions are consolidated into three functionally specialized subsystems: the ventromedial prefrontal cortex (vmPFC), the dorsomedial prefrontal cortex (dmPFC), and the PCC, adjacent PreC, and lateral parietal cortex (Raichle, 2015). Although all subsystems are involved in ToM-related processes, evidence supports the dmPFC subsystem as the one that most strongly overlaps with this cognitive ability (Spreng and Andrews-Hanna, 2015; Udochi et al., 2022).

Altered activity and connectivity on the DMN and ToM networks are associated with several mental health and neurodegenerative disorders. On the one hand, disrupted DMN activity is present in pathologies such as depression, attention deficit hyperactivity disorder, and Alzheimer’s

disease among others (Mohan et al., 2016). Therefore, this network has been studied as a possible assessment for early detection and treatment efficacy (Mohan et al., 2016). On the other hand, systematic evidence points to social cognitive dysfunction as a cognitive phenotype of many developmental, neurological, and psychiatric conditions. As a result, social dysfunction has become one of the six trans-diagnostic dimensions according to the Research Domain Criteria (RDoC) framework and a potential target for therapeutic interventions (Insel et al., 2010). Nevertheless, there is still a lack of treatment approaches specifically targeting social cognition.

Serotonergic psychedelics such as Lysergic Acid Diethylamide (LSD), psilocybin, N,N-Dimethyltryptamine (DMT), or Ayahuasca are psychoactive compounds that act as partial or full agonists of the 5HT2A receptor and are characterized by inducing changes in perception, mood, cognition, and the sense of “self” (Castelhamo et al., 2021). Recent research on these substances has suggested their potential therapeutic properties for treating pathologies such as depression, anxiety, or substance use disorder (Fuentes et al., 2020; Oliveira et al., 2022; Rodrigues et al., 2019; Thomas et al., 2017). Yet, the mechanism through which these compounds seem to elicit these effects remains unknown.

In this regard, the ability of psychedelics to modulate the sense of “self” suggests that their mechanisms could be mediated by ToM or the DMN. This is further supported by the evidence showing the modulatory effects of psychedelics on DMN and social cognition (Gattuso et al., 2022; Preller and Vollenweider, 2019). For instance, various studies depict the capacity of these compounds to positively influence aspects related to healthy social functioning like changes in personality traits such as agreeableness (Netzband et al., 2020) and compassion (Apud Peláez, 2020), feelings of connection to others (Watts et al., 2017), and increased emotional empathy and prosocial behavior (Dolder et al., 2016; Mason et al., 2019; Pokorny et al., 2017; Uthaug et al., 2021). More specifically, LSD has been shown to alter the processing of joint attention, an essential component of ToM, and increased functional connectivity in the bilateral temporoparietal junction, one of the regions shared by the ToM and the DMN (Preller et al., 2018; Tagliazucchi et al., 2016). Besides, the ability of psilocybin, LSD, and Ayahuasca to decrease the functional connectivity within the DMN and increase

Table 2

Results of meta-analyses for each individual group. The Brodmann Area (BA), ALE value of the peak activated voxel, and MNI coordinates are presented for the major activations at the cluster-level FWE-corrected threshold of $p < 0.05$, along with 1000 permutations. Additionally, statistical values are provided for each cluster.

Cluster #	x	y	z	ALE	P	Z	Hemisphere	Lobe	Label	BA
A. Social Cognition										
1	-2	-56	34	0.032945164	2.9255077E-7	4.9960938	Left	Limbic	Cingulate Gyrus	31
1	-4	-56	28	0.032918245	2.978535E-7	4.992626	Left	Limbic	Posterior Cingulate	31
1	4	-54	32	0.027511317	6.9807993E-6	4.3444705	Right	Limbic	Cingulate Gyrus	31
2	-54	-60	24	0.029172331	2.709946E-6	4.547851	Left	Temporal	Superior Temporal Gyrus	39
3	58	-2	-22	0.031256482	8.0037E-7	4.798246	Right	Temporal	Middle Temporal Gyrus	21
4	-60	-10	-14	0.034363143	1.2461598E-7	5.158307	Left	Temporal	Middle Temporal Gyrus	21
5	-44	-60	-10	0.028531248	3.91285E-6	4.469906	Left	Temporal	Fusiform Gyrus	37
6	56	-48	14	0.030795084	1.0495127E-6	4.7436633	Right	Temporal	Superior Temporal Gyrus	22
7	0	46	-18	0.032011468	5.131457E-7	4.886548	Left	Frontal	Medial Frontal Gyrus	10
7	-6	48	-4	0.021717748	1.6150877E-4	3.5961053	Left	Limbic	Anterior Cingulate	32
8	-4	56	20	0.03670967	2.9192039E-8	5.423724	Left	Frontal	Medial Frontal Gyrus	9
B. Theory of Mind (ToM)										
1	4	-52	28	0.034662727	9.739291E-9	5.6166253	Right	Limbic	Cingulate Gyrus	31
1	8	-54	26	0.03163413	7.5522806E-8	5.251314	Right	Limbic	Posterior Cingulate	31
1	-2	-50	30	0.030928435	1.2023007E-7	5.1650133	Left	Limbic	Cingulate Gyrus	31
2	-52	24	8	0.029716317	2.6639478E-7	5.0141354	Left	Frontal	Inferior Frontal Gyrus	45
3	54	-50	14	0.035200745	6.707367E-9	5.6807566	Right	Temporal	Superior Temporal Gyrus	22
4	54	-2	-24	0.032533314	4.1385583E-8	5.3610206	Right	Temporal	Middle Temporal Gyrus	21
5	-48	-58	24	0.025223615	4.6113914E-6	4.4346437	Left	Temporal	Superior Temporal Gyrus	39
6	-60	-10	-14	0.028217303	7.039233E-7	4.8239074	Left	Temporal	Middle Temporal Gyrus	21
7	-44	10	50	0.022815444	1.9786545E-5	4.1099615	Left	Frontal	Middle Frontal Gyrus	6
8	-8	54	34	0.026396438	2.2246943E-6	4.589215	Left	Frontal	Superior Frontal Gyrus	8
C. Rest / Default Mode network (DMN)										
1	0	50	-12	0.024628498	1.1803663E-7	5.168456	Left	Limbic	Anterior Cingulate	32
1	-4	40	-6	0.014278379	2.1215202E-4	3.524487	Left	Limbic	Anterior Cingulate	24
2	2	-52	26	0.022974348	4.3634225E-7	4.9183884	Left	Limbic	Posterior Cingulate	23

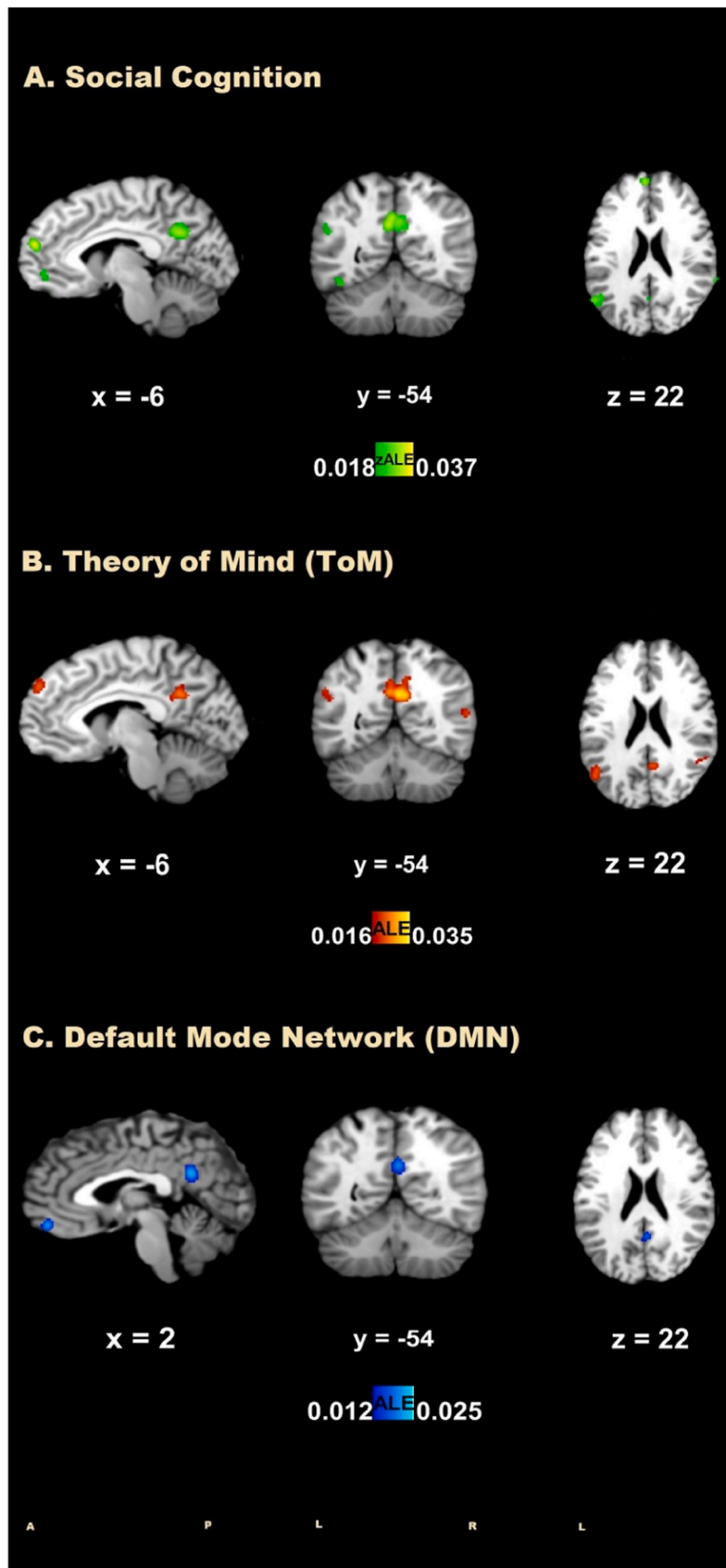


Fig. 1. Brain activation maps for (A) social cognition tasks; (B) Theory of Mind (ToM) tasks, (C) and rest conditions / Default Mode Network (DMN).

Table 3

Results of conjunction analyzes between social cognition, theory of mind (ToM) and Default Mode Network (DMN) at the default threshold of $p < 0.001$, along with 1000 permutations, and a minimum cluster size of 200 mm³. The Brodmann Area (BA), ALE value of the peak activated voxel, and MNI coordinates are presented for the major activations.

Cluster #	x	y	z	ALE	Hemisphere	Lobe	Label	BA
Social Cognition \cap DMN								
1	2	-52	28	0.021991717	Left	Limbic	Cingulate Gyrus	31
2	-2	50	-16	0.020006659	Left	Frontal	Medial Frontal Gyrus	10
2	-2	48	-10	0.016189825	Left	Limbic	Anterior Cingulate	32
3	-60	-10	-18	0.018323746	Left	Temporal	Inferior Temporal Gyrus	21
4	62	-10	-16	0.015424554	Right	Temporal	Middle Temporal Gyrus	21
5	-22	-14	-14	0.013712543	Left	Sub-lobar	*	Amygdala
6	0	56	12	0.010649103	Left	Frontal	Medial Frontal Gyrus	9
7	12	-58	26	0.010744087	Right	Limbic	Posterior Cingulate	31
8	-36	6	42	0.010430146	Left	Frontal	Middle Frontal Gyrus	6
9	4	38	-16	0.008248041	Right	Limbic	Anterior Cingulate	32
10	2	38	-14	0.008346476	Right	Limbic	Anterior Cingulate	32
ToM \cap DMN								
1	2	-52	26	0.022974348	Left	Limbic	Posterior Cingulate	23
2	-60	-10	-18	0.018323746	Left	Temporal	Inferior Temporal Gyrus	21
3	-2	50	-16	0.018057156	Left	Frontal	Medial Frontal Gyrus	10
4	60	-10	-16	0.014401572	Right	Temporal	Middle Temporal Gyrus	21
5	14	-56	26	0.012692183	Right	Limbic	Posterior Cingulate	31
6	-24	-14	-16	0.01257214	Left	Sub-lobar	*	Amygdala
7	-38	4	36	0.0119159	Left	Frontal	Precentral Gyrus	6
8	-36	6	42	0.010430146	Left	Frontal	Middle Frontal Gyrus	6
9	-36	-84	32	0.008233985	Left	Occipital	Superior Occipital Gyrus	19
10	-38	-82	32	0.009470959	Left	Temporal	Middle Temporal Gyrus	19

between-network connectivity has been claimed by different studies (Gattuso et al., 2022). In the case of psilocybin, negative correlations were found between the subjectively perceived drug intensity and plasma psilocin levels with DMN integrity (Madsen et al., 2021). Moreover, Ayahuasca decreased PCC connectivity within the DMN, a region also involved in ToM, which was seen in resting state data one day after the administration (Palhano-Fontes et al., 2015). Notably, a recent meta-analysis of brain imaging studies with classic psychedelics detected decreased connectivity within PCC/Precuneus, components of DMN, and ToM (Castelhamo et al., 2021).

Overall, the depicted evidence points to the effects on the DMN and ToM as the neural basis mediating the effects of serotonergic psychedelics. Therefore, a unified model of the overlap between both networks could help to understand the underlying mechanisms driving the clinical properties of these compounds. Nevertheless, there are still differences regarding the shared regions and functions of the DMN and ToM (Li et al., 2014; Mars et al., 2012; Schilbach et al., 2012). Consequently, this systematic review aims to provide a consolidated understanding of the overlap of these networks and thus have a more specific and updated understanding of the brain regions that connect them. Further, we will look at the overlap between these networks with those brain regions affected by psychedelics to elucidate the neuropsychological mechanisms responsible for the effects of these compounds. We hypothesize that the DMN broadly, but especially the dorsal medial subsystem, will be active during social processing tasks and that individual differences in the functions of these networks might underpin individual differences in social cognitive abilities. Additionally, we expect psychedelics to also modulate regions affected by the DMN, ToM, and social cognition, as evidence of the involvement of these brain functions in their neurocognitive mechanisms of action.

2. Methods

2.1. Search strategy and data sources

We performed the literature search using BrainMap Sleuth 3.0.4 database in December 2022. To access published brain activations related to social cognition and Theory of Mind (ToM), we followed the same search strategy as Mars et al. (2012). This approach targeted task-based fMRI studies that investigated social cognition and ToM

paradigms, the latter representing a subcomponent of social cognition. We performed separate analyses for ToM and social cognition to enable a finer focused investigation into the contributions of ToM, while considering its relationship within the broader domain of social cognition. For the DMN dataset, we implemented the search strategy outlined by Laird et al. (2009), which utilized the subtraction method to identify task-independent deactivations across various paradigms. This technique selected "deactivations" contrasts that involved baseline conditions where the signal was relatively greater than during the task condition, as well as "low-level" contrasts of resting or fixation conditions (Laird et al., 2009). Table 1 describes the search and matching criteria for each domain. The search was independently conducted by the two first authors, with validation performed by three authors.

The inclusion criteria used to select functional brain imaging studies were as follows (Eickhoff et al., 2016). 1) imaging of the entire brain; 2) reporting of coordinate-based data in a standard space, with the exclusion of review papers; 3) utilization of fMRI as the imaging method; 4) inclusion of healthy control subjects; 5) a minimum sample size of $N \geq 8$; and 6) publication within the last decade.

From the initial 329 identified studies, we included 73 fMRI studies reporting brain imaging experiments related to social cognition ($N = 33$), ToM ($N = 23$), and DMN ($N = 16$). Table 1 in the Supplementary Material provides details of the included articles, encompassing tasks and selected contrasts (see also the PRISM diagram for each group). Additionally, we incorporated the findings from our previous meta-analysis on the effects of tryptamine psychedelics on the brain (Castelhamo et al., 2021), thus adding another group to our study: psychedelics ($N = 16$). This meta-analysis included resting-state and task-based fMRI studies (see Table 2 on Supplementary Material for detailed information). The extracted brain activation foci from each of the included studies were used for the subsequent activation likelihood estimation (ALE) analysis.

2.2. ALE analysis

We manually extracted foci data from each paper and compiled it into a text file, which includes all the coordinates of the results from the original studies that met the inclusion criteria. Then, an ALE meta-analysis was performed following the procedure previously outlined by Turkeltaub et al. (2002). The primary objective of this initial step was

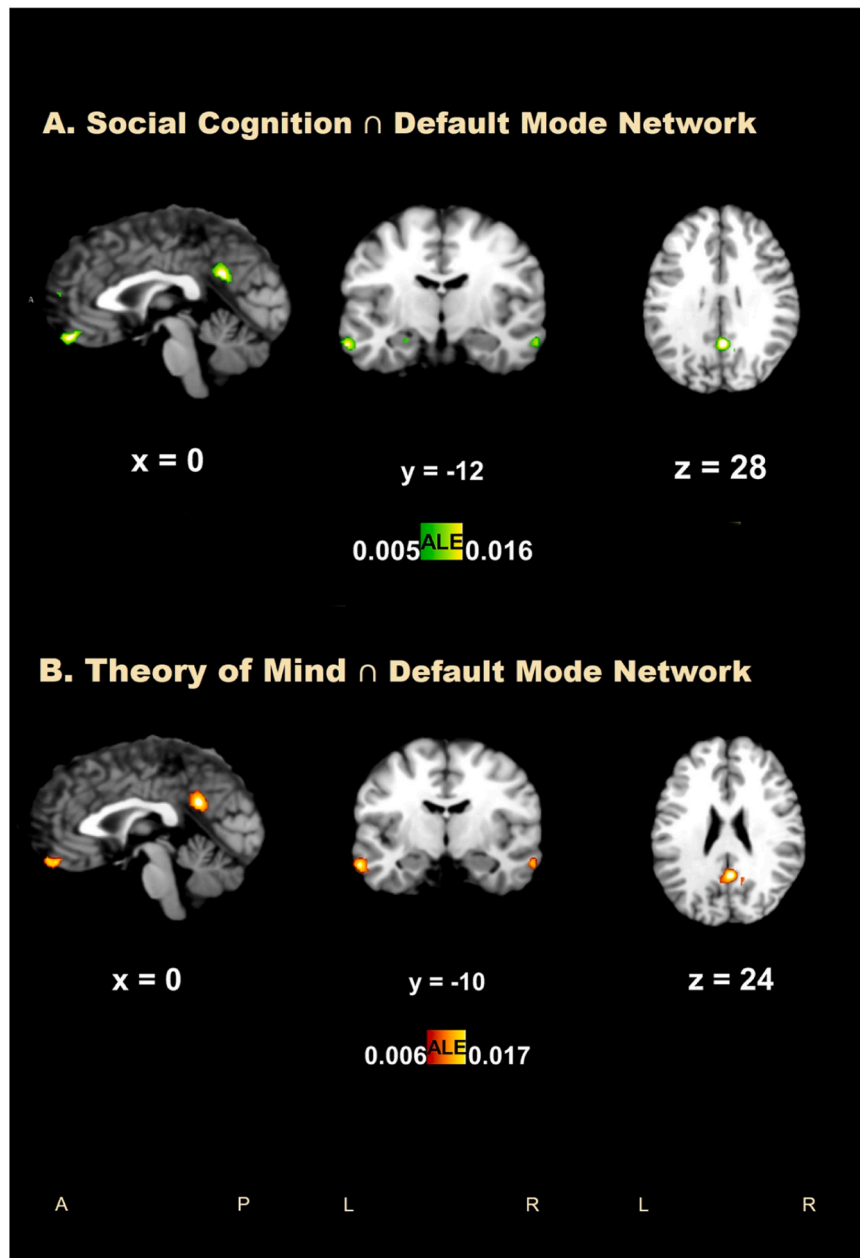


Fig. 2. Conjunction brain activation maps of (A) social cognition and Default Mode Network (DMN), (B) and of Theory of Mind (ToM) and Default Mode Network (DMN).

to localize each network individually, allowing for the subsequent overlap analysis between them. We assessed the statistical significance of the findings by applying a cluster-level family-wise error (FWE) correction with a threshold of $p < 0.05$, along with 1000 permutations. This analysis was performed using GingerALE (v3.0.2), the Java version of ALE developed at the Research Imaging Center and available at <http://brainmap.org/ale> for data processing. For visualization, the results were overlaid into a standard MNI image template (Kochunov et al., 2002).

We utilized Mango software (<http://ric.uthscsa.edu/mango/>) to overlay and exhibit activation maps associated with each task. The Talairach Daemon (<http://talairach.org/>) tool was employed to extract anatomical labels for the outcomes. All the input files utilized in the analysis, as well as the output results, can be obtained upon request from the corresponding author.

2.3. Conjunction analysis

We conducted a conjunction analysis to determine if any brain regions were activated by all task groups and psychedelics. This method measures the overlap between regions that were identified as statistically significant in the individual meta-analyses. To carry out this analysis, we utilized the "contrast datasets" function in GingerALE (v3.0.2). Our threshold for identifying significant results was set to $p < 0.001$, permutation test (1000 permutations), and a minimum cluster size of 200 mm^3 (Eickhoff et al., 2016). Through this procedure, we were able to identify brain regions that were significantly activated across the different meta-analyses.

3. Results

We performed three individual quantitative ALE meta-analyses using

Table 4

Results of conjunction analyses between social cognition, theory of mind (ToM) and psychedelics at the default threshold of $p < 0.001$, along with 1000 permutations, and a minimum cluster size of 200 mm³. The Brodmann Area (BA), ALE value of the peak activated voxel, and MNI coordinates are presented for the major activations.

Cluster #	x	y	z	ALE	Hemisphere	Lobe	Label	BA
Social Cognition \cap Psychedelics								
1	-2	-46	30	0.015930485	Left	Limbic	Cingulate Gyrus	31
1	4	-52	26	0.008191247	Right	Limbic	Posterior Cingulate	23
2	-6	44	-6	0.014054878	Left	Limbic	Anterior Cingulate	32
3	4	24	18	0.011297949	Right	Limbic	Anterior Cingulate	24
3	-2	22	28	0.008163719	Left	Limbic	Cingulate Gyrus	32
4	2	58	14	0.00866644	Left	Frontal	Medial Frontal Gyrus	9
5	-52	-48	38	0.012376023	Left	Parietal	Supramarginal Gyrus	40
6	-38	-70	-16	0.012172861	Left	Posterior	Declive	*
7	52	-66	24	0.007892478	Right	Temporal	Middle Temporal Gyrus	39
ToM \cap Psychedelics								
1	-2	-46	30	0.015930485	Left	Limbic	Cingulate Gyrus	31
1	4	-52	26	0.008191247	Right	Limbic	Posterior Cingulate	23
2	0	48	-14	0.012143315	Left	Limbic	Anterior Cingulate	32
3	52	-64	26	0.0071143033	Right	Temporal	Middle Temporal Gyrus	39
4	-46	38	20	0.0073148888	Left	Frontal	Middle Frontal Gyrus	46
5	-54	-42	38	0.007269903	Left	Parietal	Supramarginal Gyrus	40

fMRI BOLD activation for different groups: (1) social cognition, which comprised 865 activation foci from 33 studies with 791 participants; (2) theory of mind, which consisted of 675 activation foci from 23 studies with 526 participants; and (3) DMN/rest, which included 249 activation foci from 16 studies with 482 participants (see Table 1). Additionally, we incorporated the findings from our previous meta-analysis on the effects of tryptamine psychedelics on the brain (Castelhamo et al., 2021), thus adding another group to our study: (4) psychedelics, which encompassed 174 activation foci from 16 studies with 323 participants. In total, we meta-analyzed 1963 activation foci from 88 studies that included 2122 participants.

3.1. Individual meta-analysis

The meta-analysis of brain activation associated with social cognition tasks revealed several clusters of reliable activation across studies. We found significant activations in areas located in the limbic, temporal, and frontal lobes, specifically the cingulate gyrus (BA 31 and 32), middle and superior temporal gyrus (BA 39, 21, 22), and medial frontal gyrus (BA 9 and 10) ($p < 0.001$, FWE-corrected) (Fig. 1A). The section "social cognition" in Table 2 identifies the coordinates of the peak voxels for the clusters and the brain region label including statistical values.

In the individual meta-analysis of reported activations for ToM tasks, we similarly found the largest areas of activations in both the middle and superior temporal gyrus (BA 39, 21, and 22), cingulate gyrus (BA 31) and in the frontal gyrus (BA 6, 8, and 45) ($p < 0.0001$, FWE-corrected). Results are shown in Fig. 1B and Table 2B.

Concerning the rest/DMN, the recruited areas were found in the limbic lobe, namely the anterior and posterior cingulate (BA 23, 24 and 32), as shown in Table 2 C and Fig. 1C ($p < 0.001$, FWE-corrected).

Detailed information regarding the exploratory analysis for activated clusters for social cognition, ToM, and DMN at the uncorrected threshold of $p < 0.01$ and a minimum cluster size of 200 mm³ is presented in Supplementary Tables 1, 2, and 3, respectively, and in Supplementary Figure 1.

3.2. Conjunction analyzes

3.2.1. Social cognition, ToM, and DMN

To examine the shared activation among the groups, we conducted a conjunction analysis. This procedure characterized the overlap between social cognition, ToM, and DMN. First, we calculated a conjunction analysis between significant findings for social cognition and DMN at the default threshold of $p < 0.001$ (Section "Social Cognition \cap DMN" in Table 3, Fig. 2A). We found that mainly limbic areas of the cingulate cortex (BA 31 and 32, right and left) were the largest areas of joint

activation. We also identified areas located in the temporal and frontal lobes, namely the inferior and middle temporal gyrus (BA 21) and the middle frontal gyrus (BA 10, 9, and 6).

Next, we performed the same conjunction analysis for ToM and DMN activations ($p < 0.001$) (Section "ToM \cap DMN" in Table 3, Fig. 2B). We identified similar results, with a left limbic area with a peak BA 23 (cingulate gyrus) showing the highest joint activation. The right posterior cingulate (BA 31) was also identified. Similarly, we found areas of significant conjunction in the inferior and middle temporal gyrus (BA 21 and 19) and the middle frontal gyrus (BA 10 and 6). Additionally, a cluster of joint activation with its peak in the left amygdala was identified in both conjunction analyses.

3.2.2. Social cognition, ToM, DMN, and psychedelics

We then conducted a conjunction analysis between significant findings for social cognition and ToM tasks and the brain activation maps for tryptamine psychedelics (Castelhamo et al., 2021). The largest areas of joint activation for both social cognition and psychedelics and for ToM and psychedelics were found in the cingulate cortex (Brodmann areas 31, 32, and 23). We also found the middle frontal gyrus (BA 9 and 46), the middle temporal gyrus (BA 39), and the supramarginal gyrus (BA 40) as areas of joint activation. Table 4 and Figs. 3A and 3B present the clusters of activation that were significant at the threshold of $p < 0.001$.

To test our hypothesis regarding the relationship between social cognition, ToM and DMN, as well as the potential of psychedelics to elucidate this relationship, we conducted an overlap analysis among the four groups. This analysis was conducted using a voxel-level FWE-corrected threshold of $p < 0.05$, along with 1000 permutations. Similarly, the limbic areas of the cingulate cortex (BA 31), the temporal gyrus (BA 39, 21 and 22), and the frontal gyrus (BA 9, 10 and 47) showed the highest joint activation ($p < 0.00001$) (Fig. 4, Table 5).

We conducted a contrast analysis to determine the brain regions that exhibited greater activation during the psychedelic states compared to rest/DMN, and vice versa. However, we did not observe any significant results, which was unexpected given the prior claims on underactivation of DMN under psychedelics.

All analyses revealed highly similar results for ToM and social cognition, which is somewhat expected given that ToM is a large sub-domain of social cognition. Consistent with our expectations, a conjunction analysis unveiled a significant shared neural substrate between the two constructs, as detailed in Supplementary Table 6. Interestingly, no clusters showed significantly stronger activation in social cognition paradigms, highlighting the close relationship between ToM and other social cognition abilities.

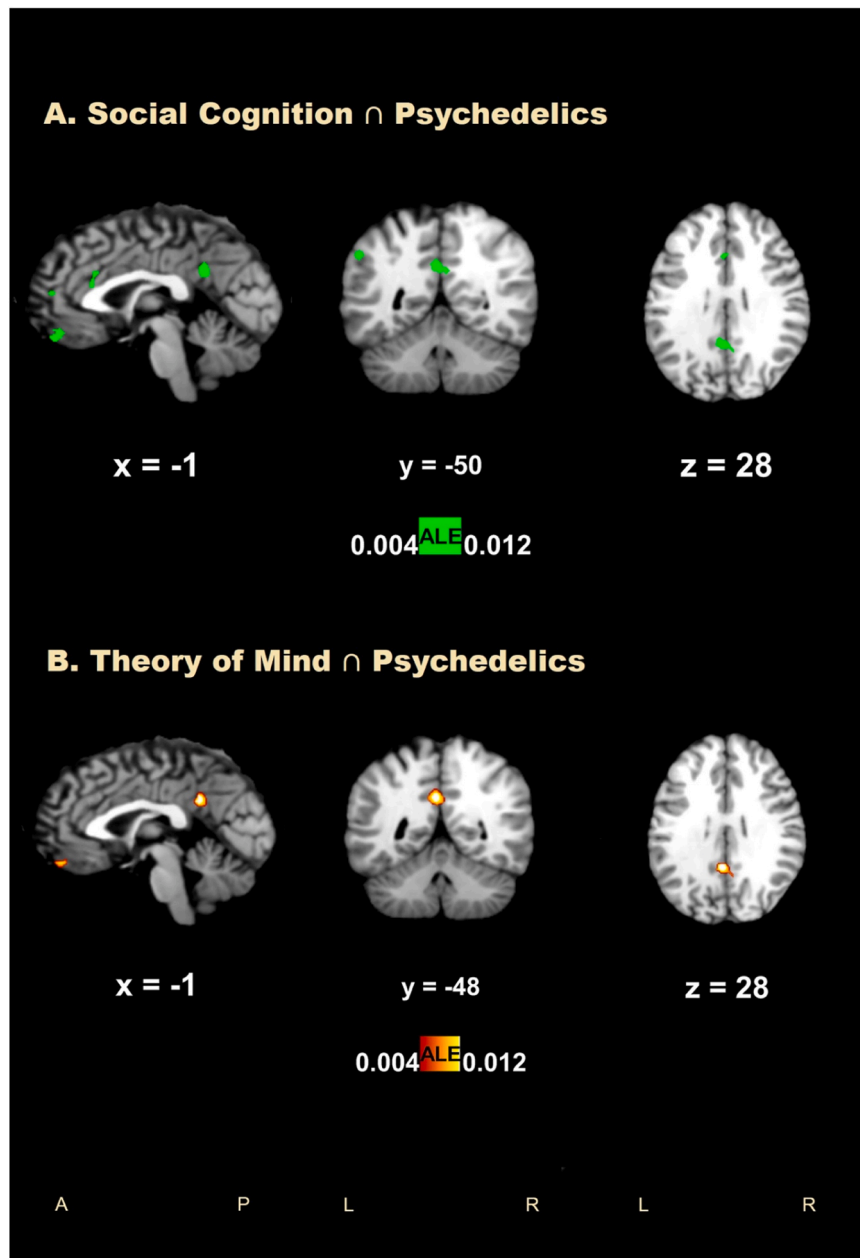


Fig. 3. Conjunction brain activation maps of (A) social cognition and psychedelics and (B) Theory of Mind (ToM) and psychedelics.

4. Discussion

This paper aimed to give insight into the overlap between social cognition and ToM with the DMN while investigating if psychedelics affect regions activated during social cognition and ToM tasks as a potential way to elucidate the mechanisms of these compounds. Our research revealed a specific set of brain regions that tend to be present in all the conjunction analyses we develop. These include the limbic areas of the cingulate cortex (largest regions of activation), as well as the middle temporal and frontal gyrus. Interestingly, psychedelics seem to share a very similar type overlap with ToM and social cognition as the DMN.

Our analysis showed that the overlap of brain regions activated during ToM tasks and rest conditions was almost the same as the one presented by tasks involving social cognition and the DMN. As a result, the DMN does not seem to play a specific role in ToM, but rather plays a general role in a broad set of social cognitive paradigms, contrary to

what might be expected. This discrepancy with our original hypothesis might be due to the similar involvement of the DMN in both brain functions, suggesting that other networks might underlie their differences. It is possible that the DMN underlies similar brain processes taking part both in ToM tasks and other tasks involving different socio-cognitive functions, or that processes associated with social cognition could be a subset for processes of ToM or vice-versa, as previously suggested. (Schurz et al., 2020). Despite this, we can conclude by stating that social cognition and ToM processes share a very specific anatomical overlap with the DMN, which corroborates previous literature on the topic (Li et al., 2014). Nevertheless, our results provide a more specific definition of this overlap highlighting the role of the cingulate cortex.

Importantly, this is the first study investigating the overlap between social cognition, ToM, and psychedelics. Notably, psychedelics seem to share with social cognition and ToM the same anatomical overlap as the DMN, involving the ACC and PCC. Intriguingly, we performed a contrast analysis on psychedelics and DMN studies and did not observe any

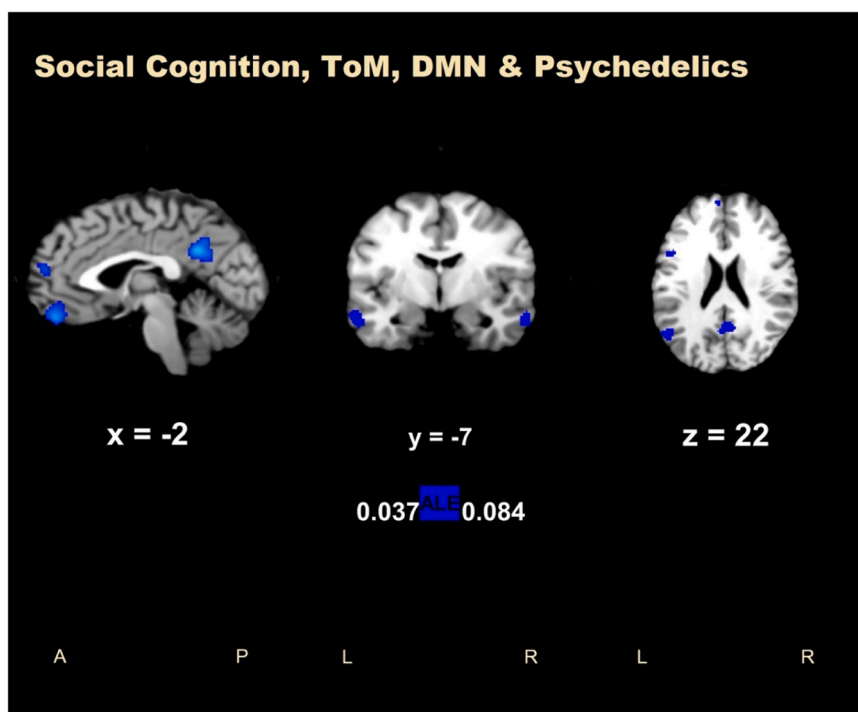


Fig. 4. Overlap of brain activation between social cognition, theory of mind (ToM), default mode network (DMN) and psychedelics.

Table 5

Overlap in brain activation across studies of social cognition, theory of mind (ToM), Default Mode Network (DMN) and psychedelics, as assessed using a quantitative meta-analysis. The Brodmann Area (BA), ALE value of the peak activated voxel, and MNI coordinates are presented for the major activations at the voxel-level FWE-corrected threshold of $p < 0.05$, along with 1000 permutations.

Cluster #	x	y	z	ALE	P	Z	Hemisphere	Lobe	Label	BA
1	2	-52	28	0.08446036	3.4267664E-17	8.35006	Left	Limbic	Cingulate Gyrus	31
1	-2	-50	30	0.07644265	5.814079E-15	7.7204165	Left	Limbic	Cingulate Gyrus	31
2	-2	48	-16	0.06930593	4.5894766E-13	7.142532	Left	Frontal	Medial Frontal Gyrus	10
3	56	-2	-24	0.06763837	1.2424212E-12	7.0043716	Right	Temporal	Middle Temporal Gyrus	21
4	-60	-10	-16	0.074186675	2.3547516E-14	7.5400515	Left	Temporal	Inferior Temporal Gyrus	21
5	-48	-58	24	0.052916214	4.9897784E-9	5.7311397	Left	Temporal	Superior Temporal Gyrus	39
5	-52	-62	32	0.037706114	9.62814E-6	4.2733493	Left	Temporal	Middle Temporal Gyrus	39
6	56	-48	14	0.06364154	1.291675E-11	6.6687202	Right	Temporal	Superior Temporal Gyrus	22
7	-4	56	18	0.054003607	2.7991138E-9	5.828409	Left	Frontal	Medial Frontal Gyrus	9
8	-44	26	-12	0.053313505	4.0516692E-9	5.766361	Left	Frontal	Inferior Frontal Gyrus	47
9	30	-92	-2	0.059237335	1.5773662E-10	6.2910943	Right	Occipital	Inferior Occipital Gyrus	18
10	-58	-38	0	0.04808798	6.215631E-8	5.287074	Left	Temporal	Middle Temporal Gyrus	22
10	-62	-30	-6	0.043106355	7.471372E-7	4.8120165	Left	Temporal	Middle Temporal Gyrus	21
11	-48	12	22	0.050172325	2.124758E-8	5.480202	Left	Frontal	Inferior Frontal Gyrus	9
12	52	6	32	0.043679398	5.6555E-7	4.8673587	Right	Frontal	Inferior Frontal Gyrus	6
12	48	10	32	0.042421237	1.0445759E-6	4.744618	Right	Frontal	Precentral Gyrus	9
13	-44	-60	-10	0.047218457	9.679784E-8	5.2054157	Left	Temporal	Fusiform Gyrus	37
14	-50	28	8	0.04474478	3.3546903E-7	4.969614	Left	Frontal	Inferior Frontal Gyrus	45

significant results, which was unexpected. This finding suggests that these compounds may not deactivate the DMN as stated by previous literature (Gattuso et al., 2022; van Elk and Yaden, 2022). One hypothesis is that psychedelics could activate certain DMN brain regions, particularly those relevant to social cognition and ToM. This finding could support the idea that social cognition and ToM may be involved in the mechanisms of action underlying the effects of psychedelics. Furthermore, these processes may also be mediated by their overlap with the DMN.

Above all, the ACC and PCC seem to be the regions where neural processing related to social cognition, ToM, DMN, and psychedelics overlap. While the ACC is associated with self-perspective (*self-evaluation*) (Hu et al., 2016; Morita et al., 2014; Yang et al., 2012), the PCC is related to episodic autobiographical memory (Boccia et al., 2019; Leech and Sharp, 2014; Maddock et al., 2001) Therefore, the action of both

regions in the overlap between social cognition and ToM with the DMN suggests that self-perspective and autobiographical memories are the brain functions linking these networks. Consequently, our results could further support those accounts in favor of a predisposition of the human species for social cognition as their default mode of cognizing (Schilbach et al., 2008), which might only relate to the role of autobiographical memories and self-perspective in the definition of the “self”. It is also important to note that psychedelics modulate other brain regions, which not emerge in our study due to our focused interest on social cognition, but that can have at least indirect relevance to the self.

Additionally, the impact of psychedelics on these overlapping neural systems suggests that these compounds influence social cognition and theory of mind by enhancing the nodes of the DMN involved in these brain functions. Therefore, due to the ability of psychedelics to induce autobiographical memories (Healy, 2021), and change self-perspective

(Amada et al., 2020), previously linked to their therapeutic potential (Hayes et al., 2019; Rodríguez-Cano et al., 2023; Yaden and Griffiths, 2021), our results also point to these psychological effects as the mediators of the impact of these on social cognition and ToM. Moreover, the ability of psychedelics to affect regions of ToM and social cognition, along with their known neuroplastic properties (Vargas et al., 2023), follows up on previous literature suggesting the potential of psychedelics to open a critical period that could allow the modulation of social reward learning circuits (Duerler et al., 2022; van Elk and Yaden, 2022). Overall, our studies support the ability of psychedelics to modulate social cognition and ToM. We hope future studies will try to give a more precise definition of the role of these brain networks in the effects of these compounds, as this could provide better insights into the nature of the self and its neural correlates. For example, fMRI studies assessing the impact of psychedelics on self-perspective (evaluation) and episodic autobiographic memories could allow a better definition of the modulation of these brain functions by psychedelic compounds. Finally, our analysis also points to the therapeutic potential of psychedelics for those diseases showing deficits in social cognition and ToM. Indeed, there is a need for clinical trials on populations showing deficits in these brain functions, as this could allow for further develop new therapies addressing this burden.

5. Limitations

This meta-analysis has some limitations, including the heterogeneity in outcome measures within theory of mind studies. The experimental tasks comprised a range of ToM tasks, such as false belief tasks, facial emotion recognition tasks, observation of videos depicting human emotional displays, and animated shapes representing social interactions. This heterogeneity could impact the meta-analysis results, although the findings were consistent with previous literature. Other limitations include studies with a non-equal gender distribution (some including only men) and small sample sizes (minimum of $N \geq 8$). However, given the overall sample size of 2122 subjects, the statistical power is sufficient to strengthen the findings.

Funding sources

This work was supported by the Foundation for Science and Technology of Portugal [grant numbers UIDB/4950/2020, UIDP/4950/2020, DSAIPA/DS/0041/2020, 2022.02963. PTDC]; the Bial Foundation, 252/2018].

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.neubiorev.2023.105325](https://doi.org/10.1016/j.neubiorev.2023.105325).

References

- Adolphs, R., 2001. The neurobiology of social cognition. *Curr. Opin. Neurobiol.* 11, 231–239. [https://doi.org/10.1016/s0959-4388\(00\)00202-6](https://doi.org/10.1016/s0959-4388(00)00202-6).
- Amada, N., Lea, T., Letheby, C., Shane, J., 2020. Psychedelic experience and the narrative self: an exploratory qualitative study. *J. Conscious. Stud.* 27, 6–33.
- Apud Peláez, I.E., 2020. Personality traits in former Spanish substance users recovered with ayahuasca. *J. Psychoact. Drugs* 52, 264–272. <https://doi.org/10.1080/02791072.2020.1752960>.
- Boccia, M., Teghil, A., Guariglia, C., 2019. Looking into recent and remote past: meta-analytic evidence for cortical re-organization of episodic autobiographical memories. *Neurosci. Biobehav. Rev.* 107, 84–95. <https://doi.org/10.1016/j.neubiorev.2019.09.003>.
- Buckner, R.L., Carroll, D.C., 2007. Self-projection and the brain. *Trends Cogn. Sci.* 11, 49–57. <https://doi.org/10.1016/j.tics.2006.11.004>.
- Byom, L.J., Mutlu, B., 2013. Theory of mind: mechanisms, methods, and new directions 7, 1–12. <https://doi.org/10.3389/fnhum.2013.00413>.
- Castelhano, J., Lima, G., Teixeira, M., Soares, C., Pais, M., Castelo-Branco, M., 2021. The Effects of Tryptamine Psychedelics in the Brain: A meta-Analysis of Functional and Review of Molecular Imaging Studies 12, 1–13. <https://doi.org/10.3389/fphar.2021.739053>.

- Corcoran, R., Frith, C.D., 2003. Autobiographical memory and theory of mind: evidence of a relationship in schizophrenia. *Psychol. Med.* 33, 897–905. <https://doi.org/10.1017/s0033291703007529>.
- Cotter, J., Granger, K., Backs, R., Hobbs, M., Looi, C.Y., Barnett, J.H., 2018. Social cognitive dysfunction as a clinical marker: a systematic review of meta-analyses across 30 clinical conditions. *Neurosci. Biobehav. Rev.* 84, 92–99. <https://doi.org/10.1016/j.neubiorev.2017.11.014>.
- Decety, J., Sommerville, J.A., 2003. Shared representations between self and other: a social cognitive neuroscience view. *Trends Cogn. Sci.* 7, 527–533. <https://doi.org/10.1016/j.tics.2003.10.004>.
- Dolder, P.C., Schmid, Y., Müller, F., Borgwardt, S., Liechti, M.E., 2016. LSD acutely impairs fear recognition and enhances emotional empathy and sociality. *Neuropsychopharmacology* 41, 2638–2646. <https://doi.org/10.1038/npp.2016.82>.
- Duerler, P., Vollenweider, F.X., Preller, K.H., 2022. A neurobiological perspective on social influence: Serotonin and social adaptation. *J. Neurochem.* 162, 60–79. <https://doi.org/10.1111/jnc.15607>.
- Eickhoff, S.B., Nichols, T.E., Laird, A.R., Hoffstaedter, F., Amunts, K., Fox, P.T., Bzdok, D., Eickhoff, C.R., 2016. Behavior, sensitivity, and power of activation likelihood estimation characterized by massive empirical simulation. *Neuroimage* 137, 70–85. <https://doi.org/10.1016/j.neuroimage.2016.04.072>.
- Frith, C.D., Frith, U., 2006. The Neural Basis of Mentalizing Minireview 531–534. <https://doi.org/10.1016/j.neuron.2006.05.001>.
- Fuentes, J.J., Fonseca, F., Elices, M., Farré, M., Torrens, M., 2020. Therapeutic use of LSD in psychiatry: a systematic review of randomized-controlled clinical trials. *Front. Psychiatry* 10. <https://doi.org/10.3389/fpsy.2019.00943>.
- Gattuso, J.J., Perkins, D., Ruffell, S., Lawrence, A.J., Hoyer, D., Jacobson, L.H., Timmermann, C., Castle, D., Rossell, S.L., Downey, L.A., Pagni, B.A., Galvão-Coelho, N.L., Nutt, D., Sarris, J., 2022. Default mode network modulation by psychedelics: a systematic review. *Int. J. Neuropsychopharmacol.* <https://doi.org/10.1093/ijnp/pyac074>.
- Happé, F., 2003. Theory of mind and the self. *Ann. N. Y. Acad. Sci.* 1001, 134–144. <https://doi.org/10.1196/annals.1279.008>.
- Hayes, S., Law, S., Malady, M., Zhuohong, Z., Bai, X., 2019. The centrality of sense of self in psychological flexibility processes: What the neurobiological and psychological correlates of psychedelics suggest. *J. Context. Behav. Sci.* 15. <https://doi.org/10.1016/j.jcbs.2019.11.005>.
- Healy, C.J., 2021. The acute effects of classic psychedelics on memory in humans. *Psychopharmacology* 238, 639–653. <https://doi.org/10.1007/s00213-020-05756-w>.
- Hu, C., Di, X., Eickhoff, S.B., Zhang, M., Peng, K., Guo, H., Sui, J., 2016. Distinct and common aspects of physical and psychological self-representation in the brain: a meta-analysis of self-bias in facial and self-referential judgements. *Neurosci. Biobehav. Rev.* 61, 197–207. <https://doi.org/10.1016/j.neubiorev.2015.12.003>.
- Insel, T., Cuthbert, B., Garvey, M., Heinssen, R., Pine, D.S., Quinn, K., Sanislow, C., Wang, P., 2010. Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. *Am. J. Psychiatry* 167, 748–751. <https://doi.org/10.1176/appi.ajp.2010.09091379>.
- Kochunov, P., Lancaster, J., Thompson, P., Toga, A.W., Brewer, P., Hardies, J., Fox, P., 2002. An optimized individual target brain in the Talairach coordinate system. *Neuroimage* 17, 922–927.
- Laird, A.R., Eickhoff, S.B., Li, K., Robin, D.A., Glahn, D.C., Fox, P.T., 2009. Investigating the functional heterogeneity of the default mode network using coordinate-based meta-analytic modeling. *J. Neurosci. J. Soc. Neurosci.* 29, 14496–14505. <https://doi.org/10.1523/JNEUROSCI.4004-09.2009>.
- Leech, R., Sharp, D.J., 2014. The role of the posterior cingulate cortex in cognition and disease. *Brain* 137, 12–32. <https://doi.org/10.1093/brain/awt162>.
- Li, W., Mai, X., Liu, C., Moran, J., 2014. The default mode network and social understanding of others: what do brain connectivity studies tell us THE DEFAULT MODE NETWORK AND SOCIAL UNDERSTANDING OF 8, 1–15. <https://doi.org/10.3389/fnhum.2014.00074>.
- Maddock, R.J., Garrett, A.S., Buonocore, M.H., 2001. Remembering familiar people: the posterior cingulate cortex and autobiographical memory retrieval. *Neuroscience* 104, 667–676. [https://doi.org/10.1016/s0306-4522\(01\)00108-7](https://doi.org/10.1016/s0306-4522(01)00108-7).
- Madsen, M.K., Stenbæk, D.S., Arvidsson, A., Armand, S., Marstrand-Joergensen, M.R., Johansen, S.S., Linnet, K., Ozenne, B., Knudsen, G.M., Fisher, P.M., 2021. Psilocybin-induced changes in brain network integrity and segregation correlate with plasma psilocin level and psychedelic experience. *Eur. Neuropsychopharmacol.* 50, 121–132. <https://doi.org/10.1016/j.euroneuro.2021.06.001>.
- Mars, R.B., Neubert, F., Maryann, P., Sallet, J., Toni, I., Rushworth, M.F.S., 2012. On the relationship between the “ default mode network ” and the “ social brain ” 6, 1–9. <https://doi.org/10.3389/fnhum.2012.00189>.
- Mason, N.L., Mischler, E., Uthaug, M.V., Kuypers, K.P.C., 2019. Sub-acute effects of psilocybin on empathy, creative thinking, and subjective well-being. *J. Psychoact. Drugs* 51, 123–134. <https://doi.org/10.1080/02791072.2019.1580804>.
- Meyer, M.L., 2019. Social by default: characterizing the social functions of the resting. *Brain*. <https://doi.org/10.1177/0963721419857759>.
- Mohan, Akansha, Roberto, A.J., Mohan, Abhishek, Lorenzo, A., Jones, K., Carney, M.J., Liogier-Weyback, L., Hwang, S., Lapidus, K.A.B., 2016. The significance of the default mode network (DMN) in neurological and neuropsychiatric disorders: a review. *Yale J. Biol. Med.* 89, 49–57.
- Molenberghs, P., Johnson, H., Henry, J.D., Mattingley, J.B., 2016. Understanding the minds of others: a neuroimaging meta-analysis. *Neurosci. Biobehav. Rev.* 65, 276–291. <https://doi.org/10.1016/j.neubiorev.2016.03.020>.
- Morita, T., Tanabe, H.C., Sasaki, A.T., Shimada, K., Kakigi, R., Sadato, N., 2014. The anterior insular and anterior cingulate cortices in emotional processing for self-face

- recognition. *Soc. Cogn. Affect. Neurosci.* 9, 570–579. <https://doi.org/10.1093/scan/nst011>.
- Netzband, N., Ruffell, S., Linton, S., Tsang, W.F., Wolff, T., 2020. Modulatory effects of ayahuasca on personality structure in a traditional framework. *Psychopharmacology* 237, 3161–3171. <https://doi.org/10.1007/s00213-020-05601-0>.
- Oliveira, L., Daldegan-bueno, D., Wießner, L., Araujo, D.B., Fernando, L., 2022. Ayahuasca's therapeutic potential: What we know – and what not. *Eur. Neuropsychopharmacol.* 66, 45–61. <https://doi.org/10.1016/j.euroneuro.2022.10.008>.
- Palhano-Fontes, F., Andrade, K.C., Tofoli, L.F., Santos, A.C., Crippa, J.A.S., Hallak, J.E.C., Ribeiro, S., de Araujo, D.B., 2015. The psychedelic state induced by ayahuasca modulates the activity and connectivity of the default mode network. *PLoS One* 10, e0118143. <https://doi.org/10.1371/journal.pone.0118143>.
- Pokorny, T., Preller, K.H., Komater, M., Dziobek, I., Vollenweider, F.X., 2017. Effect of psilocybin on empathy and moral decision-making. *Int. J. Neuropsychopharmacol.* 20, 747–757. <https://doi.org/10.1093/ijnp/pyx047>.
- Preller, K.H., Vollenweider, F.X., 2019. Modulation of social cognition via hallucinogens and “entactogens”. *Front. Psychiatry* 10. <https://doi.org/10.3389/fpsy.2019.00881>.
- Preller, K.H., Schilbach, L., Pokorny, T., Flemming, J., Seifritz, E., Vollenweider, F.X., 2018. Role of the 5-HT_{2A} receptor in self- and other-initiated social interaction in lysergic acid diethylamide-induced states: a pharmacological fMRI study. *J. Soc. Neurosci.* 38, 3603–3611. <https://doi.org/10.1523/JNEUROSCI.1939-17.2018>.
- Raichle, M.E., 2011. Restless Brain 1. <https://doi.org/10.1089/brain.2011.0019>.
- Raichle, M.E., 2015. The Brain's Default Mode Network. <https://doi.org/10.1146/annurev-neuro-071013-014030>.
- Rodrigues, A.V., Almeida, F.J., Vieira-Coelho, M.A., 2019. Dimethyltryptamine: endogenous role and therapeutic potential. *J. Psychoact. Drugs* 51, 299–310. <https://doi.org/10.1080/02791072.2019.1602291>.
- Rodríguez-Cano, B.J., Kohek, M., Ona, G., Alcázar-Córcoles, M.Á., dos Santos, R.G., Hallak, J.E.C., Bousso, J.C., 2023. Underground ibogaine use for the treatment of substance use disorders: a qualitative analysis of subjective experiences. *Drug Alcohol Rev.* 42, 401–414. <https://doi.org/10.1111/dar.13587>.
- Schilbach, L., Eickhoff, S.B., Rotarska-Jagiela, A., Fink, G.R., Vogeley, K., 2008. Minds at rest? Social cognition as the default mode of cognizing and its putative relationship to the “default system” of the brain. *Conscious. Cogn.* 17, 457–467. <https://doi.org/10.1016/j.concog.2008.03.013>.
- Schilbach, L., Bzdok, D., Timmermans, B., Fox, P.T., Laird, A.R., Eickhoff, S.B., 2012. Introspective minds: using ALE meta-analyses to study commonalities in the neural correlates of emotional processing. *Soc. Unconstrained Cogn.* 7. <https://doi.org/10.1371/journal.pone.0030920>.
- Schurz, M., Maliske, L., Kanske, P., 2020. Cross-network interactions in social cognition: a review of findings on task related brain activation and connectivity. *Cortex* 130, 142–157. <https://doi.org/10.1016/j.cortex.2020.05.006>.
- Schurz, M., Radua, J., Aichhorn, M., Richlan, F., Perner, J., 2014. Fractionating theory of mind: A meta-analysis of functional brain imaging studies 42, 9–34.
- Spreng, R.N., Andrews-Hanna, J., 2015. The default network and social cognition. *Brain Mapp. Encycl. Ref.* 3, 165–169. <https://doi.org/10.1016/B978-0-12-397025-1.00173-1>.
- Tagliazucchi, E., Roseman, L., Kaelen, M., Orban, C., Muthukumaraswamy, S.D., Murphy, K., Laufs, H., Leech, R., McGonigle, J., Crossley, N., Bullmore, E., Williams, T., Bolstridge, M., Feilding, A., Nutt, D.J., Carhart-Harris, R., 2016. Increased global functional connectivity correlates with LSD-induced ego dissolution. *Curr. Biol.* 26, 1043–1050. <https://doi.org/10.1016/j.cub.2016.02.010>.
- Thomas, K., Malcolm, B., Lastra, D., 2017. Psilocybin-assisted therapy: a review of a novel treatment for psychiatric disorders. *J. Psychoact. Drugs* 49, 446–455. <https://doi.org/10.1080/02791072.2017.1320734>.
- Tomasello, M., 2014. The ultra-social animal. *Eur. J. Soc. Psychol.* 44, 187–194. <https://doi.org/10.1002/ejsp.2015>.
- Turkeltaub, P.E., Eden, G.F., Jones, K.M., Zeffiro, T.A., 2002. Meta-analysis of the functional neuroanatomy of single-word reading: method and validation. *Neuroimage* 16, 765–780. <https://doi.org/10.1006/nimg.2002.1131>.
- Udachi, A.L., Blain, S.D., Sassenberg, T.A., Burton, P.C., Medrano, L., DeYoung, C.G., 2022. Activation of the default network during a theory of mind task predicts individual differences in agreeableness and social cognitive ability. *Cogn. Affect. Behav. Neurosci.* 22, 383–402. <https://doi.org/10.3758/s13415-021-00955-0>.
- Uthaug, M.V., Mason, N.L., Toennes, S.W., Reckweg, J.T., de Sousa Fernandes Perna, E. B., Kuypers, K.P.C., van Oorsouw, K., Riba, J., Ramaekers, J.G., 2021. A placebo-controlled study of the effects of ayahuasca, set and setting on mental health of participants in ayahuasca group retreats. *Psychopharmacology* 238, 1899–1910. <https://doi.org/10.1007/s00213-021-05817-8>.
- van Elk, M., Yaden, D.B., 2022. Pharmacological, neural, and psychological mechanisms underlying psychedelics: A critical review. *Neurosci. Biobehav. Rev.* 140, 104793. <https://doi.org/10.1016/j.neubiorev.2022.104793>.
- Vargas, M.V., Dunlap, L.E., Dong, C., Carter, S.J., Tombari, R.J., Jami, S.A., Cameron, L. P., Patel, S.D., Hennessey, J.J., Saeger, H.N., McCorvy, J.D., Gray, J.A., Tian, L., Olson, D.E., 2023. Psychedelics promote neuroplasticity through the activation of intracellular 5-HT_{2A} receptors. *Science* 379 (6633), 700–706. doi: 10.1126/science.adf0435. Epub 2023 Feb 16. PMID: 36795823.
- Watts, R., Day, C., Krzanowski, J., Nutt, D., Carhart-Harris, R., 2017. Patients' accounts of increased “connectedness” and “acceptance” after psilocybin for treatment-resistant depression. *J. Humanist. Psychol.* 57, 520–564. <https://doi.org/10.1177/0022167817709585>.
- Yaden, D.B., Griffiths, R.R., 2021. The subjective effects of psychedelics are necessary for their enduring therapeutic effects. *ACS Pharmacol. Transl. Sci.* 4, 568–572. <https://doi.org/10.1021/acpspts.0c00194>.
- Yang, J., Dedovic, K., Chen, W., Zhang, Q., 2012. Self-esteem modulates dorsal anterior cingulate cortical response in self-referential processing. *Neuropsychologia* 50, 1267–1270. <https://doi.org/10.1016/j.neuropsychologia.2012.02.010>.