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REVIEW

Whole-brain structural and functional neuroimaging of individuals who attempted suicide and people who did not: A systematic review and exploratory coordinate-based meta-analysis

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ABSTRACT

Suicide is the cause of death of approximately 800,000 people a year. Despite the relevance of this behaviour, risk assessment tools rely on clinician experience and subjective ratings.

Given that previous suicide attempts are the single strongest predictors of future attempts, we designed a systematic review and coordinate-based meta-analysis to demonstrate whether neuroimaging features can help distinguish individuals who attempted suicide from subjects who did not. Out of 5,659 publications from PubMed, Scopus, and Web of Science, we summarised 102 experiments and meta-analysed 23 of them.

A cluster in the right superior temporal gyrus, a region implicated in emotional processing, might be functionally hyperactive in individuals who attempted suicide. No statistically significant differences in brain morphometry were evidenced. Furthermore, we used JuSpace to show that this cluster is enriched in 5-HT_{1A} heteroreceptors in the general population.

This exploratory meta-analysis provides a putative neural substrate linked to previous suicide attempts. Heterogeneity in the analytical techniques and weak or absent power analysis of the studies included in this review currently limit the applicability of the findings, the replication of which should be prioritised.

1. Introduction

Suicide is a behaviour that leads to the premature death of approximately 800,000 people a year ("WHO | Suicide data," 2020). It is estimated that for each death by suicide, there are approximately 10 to 25 non-fatal suicide attempts (SAs) (Stone et al., 2021; Wasserman, 2016). In light of the epidemiological relevance of suicidal behaviours, the importance of recognising people who are at risk of death by suicide cannot be overstated. Despite the enormous amount of published literature on lifetime (Haney et al., 2012; Masango et al., 2008; Mościcki, 1997) and proximate risk factors (Berman, 2018) of suicide, we are nowhere close to predicting suicidal behaviour with accuracy, to the extent that some authors stated that "suicide is easier to prevent than to predict" (Rihmer et al., 2018), at least for specific groups of people. amongst the myriad of factors associated with an increased risk of death by suicide, the most relevant are previous SAs (Christiansen and Frank Jensen, 2007; Owens et al., 2002). Indeed, people who acted on their thoughts of death once are more likely to attempt again, as this dramatic solution to the mental pain they experienced has become cognitively more accessible (O'Connor and Portzky, 2018), and the bridge between ideation and action has already been crossed once (Norton, 2018; O'Connor, 2021). The previous factors are pivotal in ascertaining if an individual is at risk of death. However, they can only be identified through a thorough suicidal risk assessment. Mostly, this procedure is subjective and dependant on the patient's expected consequences of their statements and the patient-interviewer therapeutic alliance. Thus, it is of utmost importance to investigate if any objective finding can help the interviewer distinguish which patients are more likely to attempt suicide.

One step in this direction could be taken by examining whether

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neuroimaging findings can distinguish people who attempted suicide from those who did not. Then, if any difference emerged, it would be easier to prospectively test whether said diversity can be used to aid the suicidal risk assessment.

1.1. Previous literature on the neurobiology and neuroimaging of suicide attempts

In the last two decades, genome-wide association studies have identified polymorphisms in DNA regions associated with several neurotransmitters and growth factors in individuals who have died by suicide (Piras et al., 2022). Most of the studies that investigated neurotransmission focused on the alterations in the serotonergic and noradrenergic systems in suicide. In post-mortem studies, individuals who died by suicide displayed a reduction of noradrenergic neurons in the locus coeruleus (Arango et al., 1996; Furczyk et al., 2013; Lutz et al., 2017). Additionally, low levels of 3-methoxy-4-hydroxy-phenylglycol (MHPG – a metabolite of noradrenaline) in cerebrospinal fluid (CSF) appeared to forecast the likelihood and lethality of suicide attempts (Galfalvy et al., 2009). Death by suicide appeared to be also associated with an increase in serotonin neurons in the brainstem, as well as a higher expression of the serotonin-synthesis enzyme TPH2 (tryptophan hydroxylase 2) compared to individuals who died suddenly from other causes (Mann, 2013; Van Heeringen and Mann, 2014). Additionally, alterations in serotonin and its major brain metabolite, 5-hydroxyindoleacetic acid (5-HIAA), appeared to be independent of specific psychiatric diagnoses (Mann, 2013). The aforementioned neurotransmission alterations are better conceptualized in the stress-diathesis model (Van Heeringen and Mann, 2014). Briefly, the model postulates that environmental stressors, through different mechanisms depending on the developmental age of the individual affected, interact with trait susceptibility to increase the risk of death by suicide. Through hypothalamic-pituitary-adrenal axis abnormalities, the serotonergic receptors, particularly 5-HT_{1A}, can be downregulated leading to impaired brain trophism in developing individuals (Turecki et al., 2012). This down-regulation seems not to take place in adults, in which altered receptor functioning could stem from a different pathway (Boldrini et al., 2008; Parsey et al., 2006). Yet, for both populations, these alterations are believed to underlie susceptibility to depressive states (Miller et al., 2013; Oquendo et al., 2003; Rajkowska, 2000). People who died by suicide and were deemed to suffer from untreated depression were found to exhibit fewer mature granule neurons in the hippocampus, particularly in the dentate gyrus (Boldrini et al., 2019, 2013, 2012, 2009). It was proposed that a possible reason for a reduction in the number of neurons derived from impaired trophic effects of 5-HT1A receptor activity (Gould, 1999). These effects seemed to be especially evident in the hippocampus (Banasr et al., 2004; Radley and Jacobs, 2002; Segi-Nishida, 2017), where a reduction in 5HT1A gene expression could also interact with excessive levels of glucocorticoids in promoting neuronal cell loss (Codagnone et al., 2022). In addition, a reduction in brain-derived neurotrophic factor (BDNF) and its tropomyosin receptor kinase B (TrkB) receptor could contribute to further impaired neurogenesis (Frodl et al., 2014; Hashimoto, 2016; Zhang et al., 2016). Moreover, a study linked the genetic variations of the serotonin-transporter-linked promoter region (5HTTLPR), a gene associated with a reduced expression of the serotonin transporter, to larger thalamic volumes in individuals who died by suicide (Young et al., 2008). Other studies have also revealed that genetic variations of 5HTTLPR were associated with altered connectivity patterns between the prefrontal cortex, amygdala, and anterior cingulate, as well as white matter abnormalities (Heinz et al., 2005; Pacheco et al., 2009; Pezawas et al., 2005). The influence of the serotonergic system on brain function and suicide has been proposed to be crucial in the prefrontal cortex (Arango et al., 2002), a key region for suppressing impulsiveness (Kim and Lee, 2011; McDonald et al., 2017), but also in subcortical structures (e.g., thalamus and basal ganglia) involved in decision-making (Ryding et al., 2006). Moreover, the possible results of a disfunction of serotonergic neurons, include deficiencies in controlling the emotional responses to mental pain (Jollant et al., 2007; Van Heeringen et al., 2010). Based on the evidence of alterations in chemical, cellular and neural systems in suicidal behaviours, brain imaging, and connectivity data have been used to train and test predictive models that could identify people with or without suicidal ideation (Stumps et al., 2021). Previous studies also showed that brain regions involved in decision-making (e.g., frontal areas) or emotion regulation (e.g., temporal cortex, insula) might help discern people with a history of suicidal behaviour from those without it with good accuracy (Aguilar et al., 2008; Stange et al., 2020; Zhu et al., 2020a), thus indicating that an imaging-based approach could be leveraged to increase the accuracy of suicidal risk assessment. A crucial, frequently overlooked, aspect is that any diversity between people who attempted suicide and people who did not should be transdiagnostic, e.g., shared amongst the different mental health conditions (MHC) that the individual might be suffering from. The reasons are twofold: although mental disorders are known risk factors for death by suicide (Moitra et al., 2021), MHCs are neither a prerequisite nor sufficient to explain suicidal behaviours. Indeed, most people who die by suicide have no history of any mental health disorders (Too et al., 2019). Moreover, a large proportion of people who died had no MHC identifiable by psychological autopsy (Cavanagh et al., 2003). A similar picture emerges when considering the individuals who survived the first SA (Nock et al., 2009). Most research on the neuroimaging features of suicidal behaviours has been conducted on participants who suffered from mood disorders (Campos et al., 2021; Duarte et al., 2017; Fan et al., 2019; Rentería et al., 2017; Johnston et al., 2017; Kang et al., 2020b; Lee et al., 2016; Zhu et al., 2020a). However, it was suggested that some brain regions, such as the temporal lobe, might be shared hubs of dysfunction associated with suicidal behaviours across different MHCs (Domínguez-Baleón et al., 2018 – for a thorough review of the literature that also discusses neuroimaging findings related to suicidal ideation, see Schmaal et al., 2020). To our knowledge, this hypothesis has not been meta-analytically investigated so far. Two other previously published reviews addressed the issue of common features of suicidality across mental health conditions but included non-suicidal self-harm in the analysis (Huang et al., 2020) or, in the case of (Jollant et al., 2018), included studies that did not look for brain-wise differences, but instead focused on specific areas of the brain (such as Soloff et al., 2012) twith an inherent a sampling bias.

Therefore, we conducted this systematic review and meta-analysis to summarise the published literature to explore whether people with a history of SA have structural or functional brain differences with respect to people without such a history (NSA). Subsequently, we performed a spatial correlation analysis with neurotransmitter receptor maps (based on positron emission tomography (PET) scan atlas) to show if any of the meta-analytically identified brain regions was significantly associated with the estimated receptor expression.

Based on previous evidence, we hypothesised that individuals with a history of SA might be characterized by abnormalities in brain regions that subserve emotion regulation, decision-making, and impulse control, including the prefrontal and temporal cortex, hypothalamus, brainstem and hippocampus (Gosnell et al., 2016; Ono et al., 2002; Sequeira et al., 2009). In addition, considering the role of serotonin in impulsivity and suicidal behaviours (Åsberg, 1997; Underwood et al., 2018), we anticipated that the changes might be more prominent in regions enriched with serotonin receptors, especially in those expressing 5-HT_{1A} (Boldrini et al., 2008; Pantazatos et al., 2022; Sullivan et al., 2015), 5-HT_{2A} (Underwood et al., 2018), and serotonin transporter (Purselle and Nemeroff, 2003).

2. Experimental procedures

2.1. Protocol and search strategy

This systematic review and coordinate-based meta-analysis followed a pre-defined protocol published at (https://osf.io/fvrdx) and adhered to the procedures of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Page et al., 2021)) (see Supplementary materials for details and PRISMA Checklist (Title, 2009)). A comprehensive literature search was performed in PubMed, Scopus, and Web of Science databases, with the following keywords: ((“suicide” OR “suicidal” OR “suicidality” OR “self-harm” OR “self--injury” OR “self-directed” OR “self-mutilation”) AND (“MRI” OR “magnetic resonance” OR “magnetic resonance imaging” OR “brain imaging” OR “neuroimaging” OR “functional MRI” OR “fMRI” OR “functional magnetic resonance imaging”)) from inception until May 19, 2022. A manual search was conducted on the reference list of included studies, relevant review articles, International Clinical Trials Registry Platform. Commentaries, editorials, and reviews were excluded. No language or publication status restriction was applied.

2.2. Eligibility

Experimental, cross-sectional, case-control, and prospective magnetic resonance imaging (MRI) studies were considered eligible. Studies were included if 1) they reported the results of structural, or resting-state or task-based functional MRI (fMRI), or functional connectivity (FC), or cortical thickness (CT) of SA and NSA (age $>$ 18 years); 2) the two groups of people being compared were homogeneous in terms of MHC (e.g., people with schizophrenia (SCZ) that attempted suicide (+AS) were compared to people with SCZ who did not attempt suicide at the time of scanning); 3) the primary MHC had to be assessed with a semi-structured or structured interview and diagnosed according to the criteria listed in the Diagnostic and Statistical Manual (DSM) or the International Classification of Diseases (ICD); 4) the structural and/or functional studies reported the stereotaxic coordinates of the significant clusters of MHC+AS vs MHC-AS, as well as full details on imaging acquisition to allow an unequivocal assessment of the extent of brain coverage. 5) studies that regarded *a priori*-defined regions-of-interest (ROI) were excluded unless they were FC studies (where ROIs might be defined to study seed-to-brain connectivity). Studies that applied small volume corrections were excluded unless there was the possibility to include those clusters that reached statistical significance with whole-brain-level correction; 6) studies on task-based fMRI were grouped according to the task administered or, in case of high heterogeneity of tasks, on the cognitive domain investigated; 7) studies regarding CT were analysed separately from the other structural studies for methodological reasons (brain coverage differs between surface-based and whole-brain volumetric studies); 8) studies regarding seed-based FC were grouped according to seed localisation. Studies that investigated FC with Independent Component Analysis (ICA) were separated from studies employing a seed-based approach. In general, the following guidelines (Müller et al., 2018; Tahmasian et al., 2019) for conducting a neuroimaging meta-analysis were observed. For further details, see also the pre-registered protocol at https://osf.io/fvrdx.

2.3. Data extraction

Duplicate records were excluded. Two authors (NM, AM) independently extracted the characteristics of each eligible study and the outcome data. Any disagreement was resolved by a third author (FS). The following variables were extracted: DOI, first author, year of publication, study design, the country where the research took place, primary diagnosis of the participants, DSM version used for psychiatric assessment, sample size per group, demographics (sex, age, education, illness duration), neuroimaging analysis methods (for structural studies: voxel-based morphometry (VBM); for resting-state studies: amplitude of low-frequency fluctuations (ALFF) (static, dynamic, normalised); for FC investigations: seed localisation or ICA; for task-based investigations: task characteristics and cognitive domain), medication, comorbid substance abuse (e.g., alcohol, drugs), weeks since last SA to scan, rating scales (e.g., Hamilton Depression Rating Scale, Beck Depression Inventory-II or others), scanner magnetic field strength, software used for the analysis (e.g., SPM5, SPM8), stereotaxic coordinate system (MNI, Talairach), the direction of contrast, coordinates, statistical correction. Studies that did not report significant differences in brain volumes between the two groups (e.g., that could not pinpoint any coordinates that differentiated people with SA from NSA) could not be included in the coordinate-based meta-analysis due to methodological reasons explained elsewhere (Müller et al., 2018; Tahmasian et al., 2019). However, these studies are acknowledged in the Supplementary Appendix.

2.4. Statistical analysis

A tailored version (see the Supplementary Appendix and (Cattarinussi et al., 2019)) of the Imaging Methodology Quality Assessment Checklist (Shepherd et al., 2012) was used to assess a quality score for each study included in the coordinate-based meta-analysis (reported in Table 1), and both reviewers (NM, AM) independently assessed each study for risk of bias (reported in the Supplementary Appendix).

We performed an exploratory coordinate-based meta-analysis (CBMA) using the activation likelihood estimation program GingerALE (version 3.0.2) (Eickhoff et al., 2009). The program, when supplied with the coordinates identified by the single studies, identifies commonly activated regions (clusters) of the brain across groups. CBMAs were performed for both VBM and resting-state index experiments that compared SA and NSA. The analysis was conducted using a cluster-level inference $p < 0.05$, 1000 thresholding permutations, and a cluster-forming threshold $p < 0.001$. The more dilated (less conservative) masking option was used. To evince any clusters that did not reach statistical significance after a cluster-level family-wise error (FWE) correction, we also conducted exploratory CBMAs without correcting for multiple comparisons (no FWE) with a cluster-forming threshold of $p < 0.0001$. Images were produced with BrainNet Viewer (Xia et al., 2013). Furthermore, we used JuSpace (Dukart et al., 2021) to correlate receptor spatial localization maps based on PET scans with the brain clusters identified in this meta-analysis. A similar approach has already been implemented to link structural features to neurotransmitter maps in multiple sclerosis (Fiore et al., 2023), or to associate structural-functional features to PET scan data in heavy cannabis users (Hirjak et al., 2022). In our case, we implemented the default settings of the tool and compared one brain cluster with 14 receptor maps by setting statistical significance for the correlations at $p < 0.0035$ (Bonferroni correction).

3. Results

3.1. Selected studies

A total of 5,659 studies were identified from Scopus, Pubmed, and Web of Science. After duplicate removal, 3,451 abstracts were screened at the title and abstract level, and 229 full-texts were retrieved for in-depth assessment. We thus excluded a total of 147 reports after full-text assessment (Fig. 1), based on methodological reasons or target population (reasons for exclusion were reported in the Supplementary Appendix). Overall, we extracted data for 98 reports that met the inclusion criteria (see Methods section for further details). Some studies reported using multiple imaging modalities (e.g., VBM and resting state-fMRI), and each modality accounts for a single experiment. Thus, the number of experiments considered in this systematic review and coordinate-based meta-analysis is higher ($k = 101$) than the number of

Table 1
Characteristics of the studies included in the coordinate-based meta-analysis and quality score.

Type of measurement	Study	N (SA/ NSA)	Age (years, mean ±sd, SA/NSA)	Female% (SA/NSA)	MHC	Diagnostic Criteria	Time from SA to scan	Current SI at scan	Quality Score
VBM	Wang et al., 2020	70/128	27.5 ± 9.6/ 27.1 ± 8.3	78.5/ 72.6	BD and MDD	DSM-IV	NA	Assessed with SSI	8
	Peng et al., 2014	20/18	27.7 ± 7.2/ 31 ±7.4	65/66	MDD	DSM-IV	NA	Not reported	8.5
	Johnston et al., 2017	26/42	20.5 ± 3/20.6 ± 3.2	77/55	BD	DSM-IV	NA	Assessed with BSI; different between SA/ NSA	9.5
	Lee et al., 2016	19/19	41.9 ± 10.8/ 41.1 ± 15.1	57.9/47.4	MDD	DSM-IV	NA	Assessed with SSI; different between SA/ NSA	9
	Aguilar et al., 2008	13/24	37.1 ± 10/ 42.6 ± 10.1	0/0	SCZ	DSM-IV	NA	Not reported	8
	Jollant et al., 2018	32/34	37.2 ± 11.8/ 35.7 ± 11.9	71.9/73.5	MDD	DSM-IV	NA	Not reported	9.5
	Benedetti et al., 2011	38/19	46±11.1/ 44.5 ± 10.5	71/57.8	BD	DSM-IV	NA	Not reported	9
	Canal-Rivero et al., 2020	23/122	28.4 ± 7.7/ 29.4 ± 8.3	39.1/37.7	FEP	DSM-IV	NA	Not reported	9.5
	Wagner et al., 2011	10/15	NR	NR	MDD	DSM-IV	NA	Not reported	8
CT	Besteher et al., 2016	14/23	34.4 ± 12.1/ 28.8 ± 9.7	57/56	SCZ	DSM-IV	NA	Not reported	8.5
	Wagner et al., 2012	15/15	41±12.5/ 34.1 ± 10.5	41/34.1	MDD	DSM-IV	NA	Not reported	8.5
	Taylor et al., 2015	21/53	33.5 ± 9.1/ 37.5 ± 8.9	33.5/37.5	MDD	DSM-IV	NA	Assessed with MINI	9
rs-fMRI	Cao et al., 2016	35/18	20.6 ± 3.6/ 21.4 ± 3	71.4/55	MDD	DSM-IV	1–6 months	Assessed with SSI	9.5
	Tian et al., 2021	42/57	27.3 ± 8.3/ 29.3 ± 9.3	66.6/56.1	BD-II	DSM-IV-TR	During the episode	Not reported	9
	Cao et al., 2015	19/20	19.8 ± 1.6/ 20.3 ± 1.7	52.6/60	None	DSM-IV	During the episode	Not reported	9.5
	Fan et al., 2013	27/9	34.4 ± 12.9/ 38.4 ± 12.5	59.2/55.5	MDD	DSM-IV	NA	Not reported	9.5
	Wagner et al., 2021	53/40	38±11.1/ 37 ±12.2	85/77.5	MDD	DSM-IV	NA	Assessed with HAMD and BDI suicidality items	9.5
	Gong et al., 2020	20/35	27.3 ± 8.3/ 23.7 ± 7	65/51.4	BD-II	DSM-IV	NA	Assessed with BSI	9
FC	Kang et al., 2017	19/19	42±10.8/ 41.1 ± 15.2	57.9/47.4	MDD	DSM-IV	NA	Assessed with SSI	9.5
	Zhang et al., 2021	88/113	26.1 ± 9.5/ 28.2 ± 9.4	78.4/71.7	BD and MDD	DSM-IV	NA	Assessed with clinical interview	8.5
	Cheng et al., 2021	30/82	23.5 ± 5.3/ 24.3 ± 8.8	63.3/63.4	BD-I	DSM-IV	NA	Not reported	8.5
	Chen et al., 2021	15/35	34±14/35±13	66.6/42.8	MDD	DSM-IV	1 month	Not reported	8.5

BD = Bipolar Disorder; BDI = Beck Depression Inventory; BSI = Beck Suicidal Ideation Scale; CBMA = Coordinate-based meta-analysis; CT = Cortical Thickness; DSM = Diagnostic and Statistical Manual of Mental Disorders; FC = Functional connectivity; FEP = First-episode psychosis; FEW = Family-wise error; GMV = Grey matter volume; HAMD = Hamilton Depression Rating Scale; MDD = Major Depressive Disorder; MHC = Mental health condition; MINI = Mini International Neuropsychiatric Interview; NSA = Individuals with no previous suicide attempts; NSA = Non-suicide attempt; rs-fMRI = Resting-state functional magnetic resonance imaging; SA = Suicide attempts; SCZ = Schizophrenia; SI = Suicidal Ideation; SSI = Scale for Suicidal Ideation; VBM = Voxel-based morphometry.

reports analysed. Six experiments focused on altered CT, while 16 experiments used VBM to evince cortical, subcortical, or cerebellar structural differences. A total of 79 experiments investigated functional differences in the target populations: 11 experiments used resting state-fMRI index, 29 used fMRI while participants were performing a task, and 39 experiments investigated FC differences. Due to methodological reasons of the retrieved studies, not all experiments were considered in an exploratory CBMA. The reasons for exclusion are reported in the appropriate experiment section below. We extracted and meta-analysed data from 22 experiments investigating the structural differences between SA and NSA. The quality of the included studies, according to an adapted version of the Imaging Methodology Quality Assessment Checklist (Supplementary Appendix and (Cattarinussi et al., 2019; Shepherd et al., 2012)), is reported in Table 1.

3.2. *All-effects (Functional imaging + morphometry) coordinate-based meta-analysis*

First of all, we pooled all the resting-state fMRI, VBM, and CT studies. Then, we meta-analysed them to identify any brain cluster of neural abnormalities across the neuroimaging modalities. We excluded task-based studies due to the heterogeneity of tasks adopted by the single reports, and FC investigations for methodological reasons (eligible connectivity indexes were seed-based and thus incomparable to whole-brain indexes). A total of 18 experiments were pooled and 93 brain foci meta-analysed. This analysis comprised 1,034 participants, 497 with a history of previous SA(s) and 537 NSA. However, no brain clusters were significantly different between SA and NSA in terms of neural activity at the multimodal level. Significant brain differences between SA and NSA, according to the single imaging modality, are summarised in the following section. Table 2 recapitulates the non-statistically significant results from the CBMAs for each brain imaging modality, which are also extensively reported and discussed in the Supplementary Appendix,

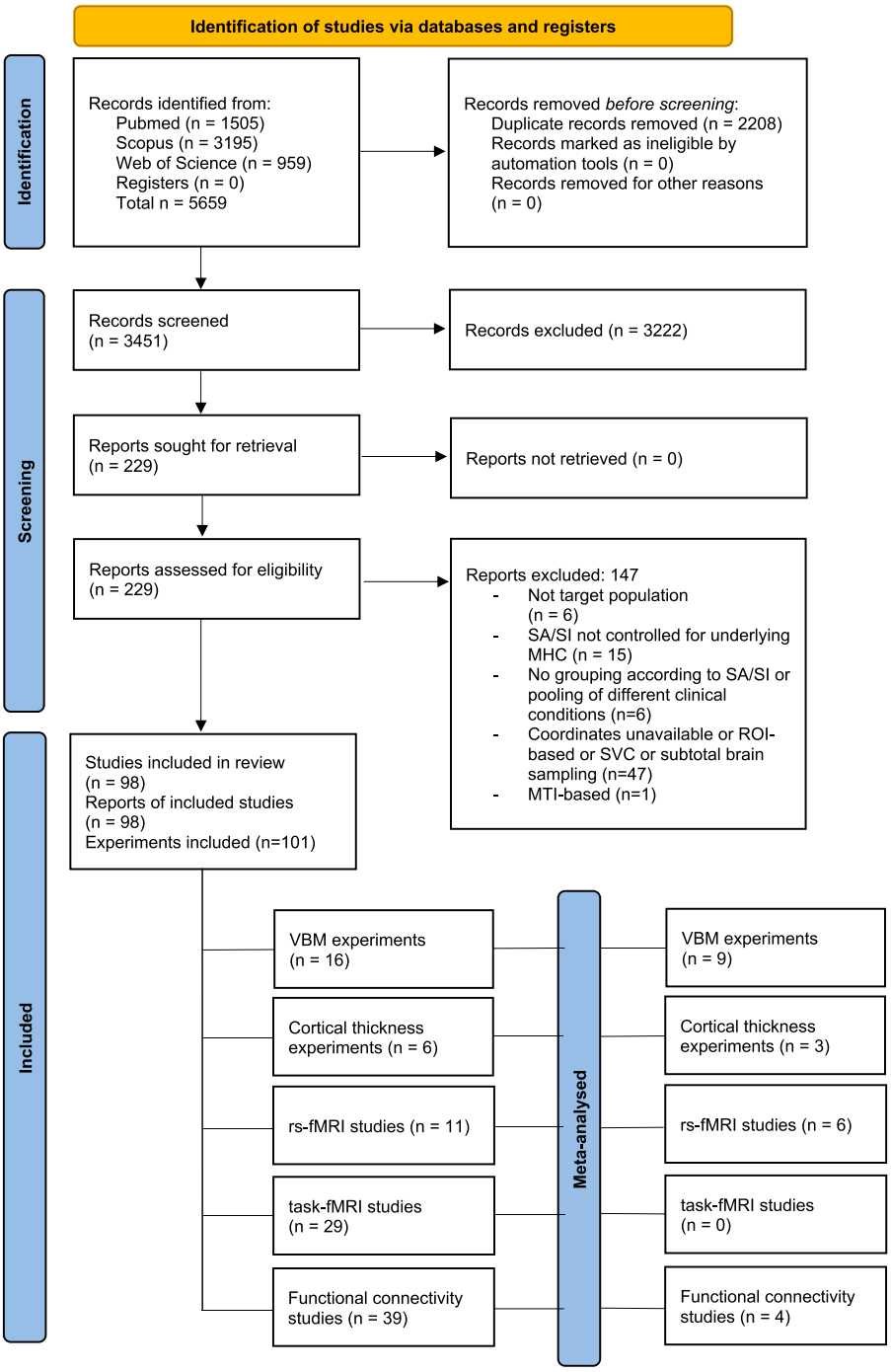

Fig. 1. PRISMA flowchart. SA = Suicide Attempt; SI = Suicidal Ideation; MHC = Mental Health Condition; ROI = Region-of-Interest; SVC = Small Volume Correction; MTI = Magnetization Transfer Imaging; VBM = Voxel-based Morphometry; rs-fMRI = Resting-state functional Mangetic Resonance Imaging.

along with CBMAs conducted for each psychiatric diagnosis separately.

3.3. Voxel-based morphometry findings

We extracted data for the exploratory CBMA (Aguilar et al., 2008; Benedetti et al., 2011; Canal-Rivero et al., 2020; Johnston et al., 2017; Jollant et al., 2018; Lee et al., 2016; Peng et al., 2014; Wagner et al., 2011; Wang et al., 2020) from nine VBM studies, all published between 2008 and 2020. No significant spatial overlap between the reported brain regions could be identified at a $p < 0.0001$ with a cluster-volume of 200 mm^3 without any statistical correction. Notably, seven eligible studies (Cao et al., 2016; Duarte et al., 2017; Fan et al., 2019; Jia et al., 2010; Kim et al., 2015; Lippard et al., 2019; Rüsch et al., 2008) did not find any significant GMV differences between SA and NSA.

3.4. Cortical thickness findings

Three studies that analysed CT differences between people with and without SA were eligible to be included in an exploratory CBMA (Besteher et al., 2016; Taylor et al., 2015; Wagner et al., 2012). As for the CBMA based on the brain morphometry, no significant spatial overlap between the coordinates of the CT differences could be identified at a $p < 0.0001$ with a cluster-volume of 200 mm^3 (and without applying any statistical correction for multiple comparisons). Moreover, all the

Table 2
Summary of single imaging modality CBMAs findings.

Imaging modality	No. studies eligibile	No. studies included in CBMA	Sample size (SA/NSA)	Statistical Significance	Other comments
VBM	16	9	251/421	No	All the significant volumetric differences except for two foci, identified smaller regional volumes in SA. Seven eligible studies did not find significant GMV differences between SA and NSA.
CT	6	3	40/91	No	Two studies did not find significant differences between the two groups after correction for multiple comparisons. All clusters ($n = 7$) identified by these three eligible studies reported reduced CT in SA.
Task-based fMRI	29	0	NA	NA	None of the task-based fMRI studies retrieved could be compared, as per methodology, to each other.
rs-fMRI	11	6	196/179	Yes	A cluster belonging to the right superior temporal gyrus survived the FWE correction
FC	39	2 + 2	45/117	No	Two studies used amygdalae as seed regions (but one found significant connectivity differences related to the left amygdala, the other one regarding the right amygdala. Thus, they could not be meta-analysed together)

CBMA = Coordinate-based meta-analysis; CT = Cortical Thickness; FC = Functional connectivity; fMRI = Functional magnetic resonance imaging; FWE = Family-wise error; GMV = Grey matter volume; NA = Not applicable; NSA = Individuals without previous -suicide attempts; rs-fMRI = Resting-state functional magnetic resonance imaging; SA = Suicide attempts; VBM = Voxel-based morphometry.

clusters ($n = 7$) identified by these three studies reported reduced CT in SA.

3.5. Task-based fMRI findings

None of the task-based fMRI studies ($k = 29$) retrieved could be compared to each other (none of the studies implemented the same task), not even when pooling studies that investigated the same cognitive domain with different tasks (see the Supplementary Appendix for reasons for exclusion of each study).

3.6. Resting-state fMRI findings

A total of 11 studies were assessed for possible pooling in the meta-analysis. We excluded five studies due to the target population of the investigations (see the Supplementary Appendix for full details). Five of the remaining six studies were conducted in China (Cao et al., 2016, 2015; Fan et al., 2013; Gong et al., 2020; Tian et al., 2021), only one (Wagner et al., 2021) was a multi-centre study conducted across Western countries (Canada, USA, Germany). Three studies (Cao et al., 2016; Fan et al., 2013; Wagner et al., 2021) included people with major depressive disorder (MDD), two studies (Gong et al., 2020; Tian et al., 2021) individuals with bipolar disorder (BD) type II, and one (Cao et al., 2015) people with a history of SAs and no recognizable MHC. A total of 196 individuals with a history of SA(s) and 179 diagnosis-matched patient controls were included in this exploratory meta-analysis, with a mean age ranging from 19.8 to 38.4 years and a percentage of females in the samples ranging from 51.4 to 85 %. Five studies used the ALFF as a measure of spontaneous brain activity, while one study employed regional homogeneity to explore local FC. A total of 37 foci coordinates were retrieved and meta-analysed: 15 foci related to spontaneous hyperactive regions in individuals with a history of suicidal behaviour, and 22 related to regions of spontaneous hypoactivity. A cluster of 520 mm^3, showing greater intrinsic activity in people with a history of SA, and belonging to the right superior temporal gyrus (rSTG) (Brodmann Area 22; Talairach space coordinates – x; y; $z = 53$; −20; 4; Fig. 2), survived FWE correction and was thus considered to be statistically significant. No brain clusters of regional hypoactivity in SA could be identified. We also conducted a CBMA for each psychiatric diagnosis (MDD and BD-II – the number of studies available for these diagnoses was greater than one) and direction of contrast (NSA>SA or SA>NSA). For MDD studies ($n = 3$) and BD ($n = 2$) studies, no brain clusters could be identified at a $p < 0.0001$ with a cluster-volume of 200 mm^3 without any statistical correction for multiple comparisons.

We implemented JuSpace (Dukart et al., 2021) to correlate the coordinates of the aforementioned brain cluster with receptor spatial localisation maps based on PET scans. We found that the cluster in the rSTG was significantly correlated ($R = 0.35$, $p = 0.003$; Fig. 2) with the 5-HT_{1A} receptor density as evidenced in (Savli et al., 2012).

3.7. Resting-state and task-based FC findings

Of the studies ($k = 39$) investigating whole-brain FC that could have been considered in a CBMA, only two pairs of studies could be compared, as per methodology, to each other ((Z. Chen et al., 2021; Cheng et al., 2021) – see Supplementary Appendix for reasons for exclusion). However, no significant spatial overlap between the coordinates of the clusters identified from the previously cited studies could be identified at a $p < 0.0001$ with a cluster volume of 200 mm^3 (and without applying any statistical correction for multiple comparisons).

Five studies used bilateral amygdalae as seed regions (Johnston et al., 2017; Kang et al., 2017; Wang et al., 2020; Zhang et al., 2021; Zhu et al., 2020b). However, for methodological reasons, none could be compared to each other in an exploratory CBMA (see Supplementary Appendix).

4. Discussion

SAs are preventable behaviours that usually emerge when individuals think of death as the only option to escape unbearable suffering (Pompili et al., 2008). Although several public health interventions can be implemented to prevent suicide at the population level (Hofstra et al., 2020; Hou et al., 2022; Mann et al., 2021), and psychotherapeutic (Brown et al., 2005; Büscher et al., 2020; Stanley and Brown, 2012) or pharmacological approaches (Baldessarini et al., 2006a; Zalsman et al., 2016) can be successfully implemented at the individual level, clinical tools to predict who is more likely to attempt suicide are somewhat limited, and mainly subject-dependant (Haney et al., 2012). In this context, neuroimaging markers bear the essential properties of representing fruitful objective measures of one's risk of death by suicide (Sudol and Mann, 2017). Thus, this systematic review and exploratory CBMA investigated brain markers potentially associated with suicide attempts. We assessed for eligibility approximately 180 studies and reviewed 101 experiments regarding differences in brain morphology or function between individuals who attempted suicide and people who did not. Despite the large number of eligible studies, most results could not be compared due to methodological reasons, especially studies on FC and task-based fMRI. Almost all the literature retrieved for this systematic review, and all the studies included in this meta-analysis, adopted a case-control study design: neuroimaging indexes of individuals who attempted suicide (SA) in the past were compared to patient controls (e.g., people that shared the same MHC with individuals with SA but never attempted suicide) or healthy controls in case that no

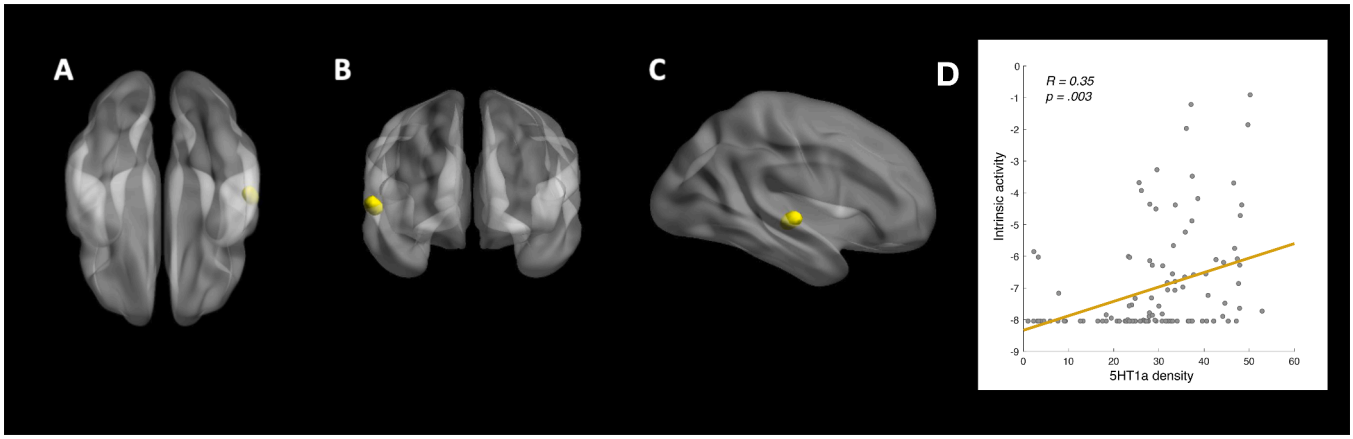

Fig. 2. A cluster in the right superior temporal gyrus showed greater intrinsic activity in people who attempted suicide and was associated with the serotoninergic signaling. Statistical maps of increased likelihood of intrinsic brain activity are rendered on an MNI template: A) Bottom view; B) Frontal view; C) Lateral (right) view. The cluster peak belongs to Brodmann Area 22; stereotaxic Talairach coordinates of the peak – x; y; z = [53;−20;4]) D) Correlation between 5-HT_{1A} receptor density and intrinsic activity (both measured in arbitrary units) . 5-HT_{1A} = serotonergic (hetero)receptor 1A. MNI= Montreal Neurological Institute

MHC could be identified in people with SA (Cao et al., 2015). The low likelihood of retrieving neuroimaging studies that prospectively investigated the neuroimaging markers of SAs is swiftly explained: SAs are rare events; this extreme behaviour is frequently the cause of the first psychiatric assessment; neuroimaging studies must have sufficient power to produce clinically meaningful results. All these factors imply that the sample sizes required to predict the first suicidal behaviour based on neuroimaging markers are prohibitive (larger sample sizes must be scanned to include people who will attempt suicide).

Nonetheless, knowing if people with a history of previous SA differed from controls in neuroimaging features could inform prediction strategies. Moreover, localising these regions of difference could provide fruitful entry points to understanding the neurophysiological pathways to suicide. Lastly, a history of previous SAs is the single strongest predictor of future SAs (Berman, 2018; Christiansen and Frank Jensen, 2007; Nordström et al., 1995). This epidemiological evidence supports the view that the identification of neuroimaging markers in individuals who have already attempted suicide could become clinically helpful to objectively assess the risk of future attempts. In essence, while the challenges of conducting prospective neuroimaging studies in the context of suicide are substantial, such research could provide valuable insights into predicting and ultimately preventing suicide attempts. Suicide risk prediction is a multi-faceted area of precision psychiatry (Salagre and Vieta, 2021), where the implementation of (neuro)biological markers in the assessment of risk could ameliorate clinical judgement (as for prognosis accuracy for psychotic transition (Koutsouleris et al., 2021)), although it should be recognized that the level of accuracy, at present, might yield an upper ceiling effect (Fusar-Poli et al., 2022), due to the vast heterogeneity intrinsic to the phenomenon itself (stemming for example, but not limited to, from cultural, familiar, personal, attitudes towards death as well as the medical and psychological history of the patient). The region identified in this CBMA, and more likely the neural circuits to which it belongs to, should be seen as a fruitful entry-point, that needs prospective corroboration, for the implementation of neuroimaging data with clinical interviews in the study of suicide risk assessment.

4.1. The right superior temporal gyrus as a region of interest in understanding suicidal behaviour

Our exploratory CBMA, based on 22 experiments, did not highlight any brain morphological differences amongst the groups of interest. However, we identified a cluster of regional hyperactivity during resting-state fMRI in the rSTG in SA. This brain region is implicated in emotion perception (S. Chen et al., 2021; Robins et al., 2009), spatial processing (Gharabaghi et al., 2006; Shah-Basak et al., 2018), and prediction of goal-directed movements of objects (Schultz et al., 2004) in healthy subjects and its activity can be modulated by the antidepressant bupropion (Hama et al., 2021). In line with the evidence pinpointing this region as a hub for goal prediction, a magnetoencephalography study highlighted the possible role of the rSTG in sustaining working memory activity (Park et al., 2011). On the other hand, studies involving subjects with MHCs evidenced that the rSTG could play a role in illness insight (Fan et al., 2017) or could be a key region functionally connected to the default mode network, mediating metabolic dysfunction and mood across the lifespan (Portugal-Nunes et al., 2021). When considering those individuals who acted on their thoughts of suicide, there were also reports of morphometric differences in the rSTG (McLellan et al., 2018; Pan et al., 2015; Sarkinaite et al., 2021), the volume of which can be influenced by lithium treatment (Benedetti et al., 2011; Eugene et al., 2014). Some studies eligible for this systematic review also identified volumetric reductions in the rSTG in SA compared to NSA (Benedetti et al., 2011; Canal-Rivero et al., 2020; Peng et al., 2014). However, the foci were too spatially segregated to be meta-analytically considered as belonging to the same cluster.

Similarly, two of the three eligible studies investigating CT (Besteher et al., 2016; Taylor et al., 2015) pinpointed the rSTG as a region with a statistically significant reduction of CT in SA. When considering the survivors of suicide loss, Jollant and colleagues (Jollant et al., 2018) highlighted a reduced volume of the temporal gyri in people with a family history of suicide, possibly indicating a neural substrate of susceptibility to suicidal behaviour (O'Connor, 2021). Regarding functional indexes of brain activation, another report that identified a cluster of hyperactivation in the STG of patients with a history of SA (Fan et al., 2013). However, this regional activation was spatially distant from the two foci (Cao et al., 2016; Gong et al., 2020) that make up the cluster identified by this exploratory CBMA. Moreover, there were reports of altered activation of the rSTG in individuals with non-suicidal self-injury (NSSI) (Huang et al., 2021; Osuch et al., 2014) and altered FC of this region with other brain regions during conflict and prediction errors (Harms et al., 2019; Minzenberg et al., 2015). Pertaining to the involvement of the rSTG in non-suicidal self-injury, we believe that the role of this region in the acquisition of capability to attempt suicide (e.g., transitioning from ideation – or NSSI – to SAs, as theorised in the Interpersonal Theory of Suicide (Joiner and Jr, 2005)) is a hypothesis worth of further investigation. Joiner hypothesised that the transition from suicidal ideation to suicide attempt could also occur through physical pain insensitivity or enhanced endurance to pain (Joiner and

Jr, 2005). This condition is more likely to occur as chronic self-injurious behaviours become less capable of regulating negative emotions (Grandclerc et al., 2016).

4.2. The right superior temporal gyrus is enriched in 5-HT$_{1A}$ receptors

We used JuSpace to evince the most represented receptors in the brain cluster belonging to the rSTG. We highlighted a significant spatial overlap between the localisation of 5-HT$_{1A}$ receptors and the cluster we identified. 5-HT$_{1A}$ can either be auto- or hetero-receptors. Autoreceptor activation plays a pivotal role in limiting the release of serotonin via a negative-feedback mechanism (Garcia-Garcia et al., 2014). In contrast, the function of heteroreceptors is less clear, although they are widely expressed in key brain regions for emotion regulation (Riad et al., 2000). It had previously been reported that people with MDD who died by suicide had lower expression of 5-HT$_{1A}$ autoreceptors in the midbrain (Boldrini et al., 2008) and were more likely to yield a polymorphism in the promoter region of the receptor gene (Lemonde et al., 2003). In the case of the localisation of this brain cluster, the spatial correlation we evidenced is more likely due to the expression of 5-HT$_{1A}$ heteroreceptors (typically expressed in the neocortex) in the rSTG rather than autoreceptors (which are usually expressed in the midbrain – dorsal raphe nuclei). Taking these pieces of evidence together, it could be likely that the putative role of the 5-HT$_{1A}$ in this region might be dissociated from depression or anxiety severity, but rather be associated with emotion regulation. However, to our knowledge, the role of 5-HT$_{1A}$ heteroreceptors in suicide has not yet been investigated. Their role might have been overshadowed by the association of 5-HT$_{1A}$ autoreceptors with depression and thus by the misconception that every person who died by suicide might have suffered from (DSM-defined) major depressive disorder (O'Connor, 2021). Given 1) the above-mentioned and further evidence of the role of serotonergic receptors in suicide and affective disorders, 2) the fact that we evidenced a spatial clustering of 5-HT$_{1A}$ receptors in the rSTG, a brain region with a role in emotion regulation, goal-directed activity, and 3) the volume of which is associated with lithium therapy (an element with potential anti-suicidal properties (Baldessarini et al., 2006b)), these four instances point at a higher likelihood that this meta-analytical finding might not be incidental and that the rSTG could represent a hub of the neural circuitry implicated in suicide. Thus, the study of 5-HT$_{1A}$ heteroreceptors role, specifically of those expressed in the rSTG, in people who attempted suicide should be prioritised as it might inform therapeutic strategies for secondary, and hopefully primary, prevention of suicidal behaviours.

4.3. Limitations

Several factors limit the results of this study. Despite using a predefined protocol that led to the inclusion of methodologically sound studies, there were multiple sources of heterogeneity: some studies compared brain function or morphometry of individuals who attempted suicide with individuals who did not, irrespective of current suicidal ideation, whereas other studies compared people who attempted suicide and have current suicidal ideation with people with only suicidal ideation but who did not act on their thoughts. The MRI scanners employed to acquire the brain images differed across the locations (in the manufacturer, the number of head coils, and the magnetic field strength), and so did the pipelines of analysis that the authors applied. Moreover, the time from suicide attempts to scan varied across the studies (although most articles did not report this information): this could be why some studies did not identify differences in brain function of people who attempted suicide in their lifetime with respect to patient controls. Regarding the heterogeneity in the demographics of the samples being studied, the mean age varied greatly (and according to the population of reference, e.g., younger patients with first-episode psychoses and older patients with MDD were included in this meta-analysis), as well as the criteria of inclusion/exclusion of individuals with active or past alcohol/substance use disorders (AUD/SUD, most of the studies enroled individuals with a history of AUD/SUD as long as the subjects had been unexposed to substances for the last 1–6 months before the scan). Moreover, the medication status of the participants, which is often an overlooked confounding factor influencing neural structure and function (Ilzarbe and Vieta, 2023), was the same across the studies: most of the participants who attempted suicide were receiving a psychotropic medication other than benzodiazepine at the time of the scan. Amongst the studies included in the CBMA, only two (Cao et al., 2015; Wagner et al., 2011) did not clearly state the current medication status of participants with a history of suicide attempts; on the other hand, (Canal-Rivero et al., 2020) specified that participants with first-episode psychosis were unexposed, or exposed for less than six weeks, to antipsychotics in their lifetime; (Gong et al., 2020) recruited participants who were unmedicated for at least six months before the scan; (Tian et al., 2021) enroled patients who had been off of medications for at least two weeks. Given the paucity of studies (for ethical reasons) that enroled unmedicated participants with a history of suicide attempts, we could not account for the role of medication on neural structure or function.

In addition, a consideration on survival bias needs to be mentioned: half of the individuals who die by suicide lose their life at their first attempt. Thus, it is impossible to know if the population that loses their lives at the first attempt differs in brain functionality from those who survive. Lastly, it is important to note that we tested the spatial correlation between the rSTG and the estimates of the neurotransmitter systems derived from PET studies conducted in healthy subjects. Future studies exploring neurotransmitter maps in individuals who attempted suicide might help clarify whether the rSTG is also enriched in 5-HT$_{1A}$ receptors in this population.

Conclusions

Taken together, this meta-analysis pinpoints a cluster in the rSTG, enriched with 5-HT$_{1A}$ receptors, the activity of which differs between individuals with a history of suicide attempts and those without. This cluster of the rSTG needs to be replicated by further studies, as it derives from the analysis of individuals from East Asia, for whom differences in the morphometry of the right superior temporal gyrus have been reported (D.W. Kang et al., 2020). At present, the rSTG cluster that we identified might yield information on the neural substrate underlying suicide, and further investigations on its functional activity and circuitry might provide relevant clinical information for suicide behaviour prediction in the future. Moreover, this systematic review highlighted that the rSTG could represent a brain region with reduced grey matter volume in people who attempted suicide. However, the foci of morphological difference identified by single studies are too spatially distant to be included in the same brain cluster. Future research should consider the presence of suicidal ideation and its severity, apply statistical corrections at the whole-brain level, employ reproducible and verified pipelines of analysis, and be based on a pre-registered protocol with a detailed power analysis.

Ethical approval

Not applicable

Data and materials availability

All data can be retrieved from the manuscript or the supplementary appendix.

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Declaration of Competing Interest

All the authors declare none.

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Supplementary materials

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