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Measurement of brain glutathione with magnetic Resonance spectroscopy in Schizophrenia-Spectrum disorders — A systematic review and Meta-Analysis

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ABSTRACT

Oxidative stress may contribute to declining course and poor outcomes in psychosis. However, in vivo Magnetic Resonance Spectroscopy studies yield disparate results due to clinical stage, sample demographics, neuroanatomical focus, sample size, and acquisition method variations. We investigated glutathione in brain regions from participants with psychosis, and the relation of glutathione to clinical features and spectroscopy protocols. Meta-analysis comprised 21 studies. Glutathione levels did not differ between total psychosis patients (N = 639) and controls (N = 704) in the Medial Prefrontal region (k = 21, d = -0.09, CI = -0.28 to 0.10, p = 0.37). Patients with stable schizophrenia exhibited a small but significant glutathione reduction compared to controls (k = 14, d = -0.20, CI = -0.40 to −0.00, p = 0.05). Meta-regression showed older studies had greater glutathione reductions, possibly reflecting greater accuracy related to spectroscopy advancements in more recent studies. No significant effects of methodological variables, such as voxel size or echo time were found. Reduced glutathione in patients with stable established schizophrenia may provide novel targets for precision medicine. Standardizing MRS acquisition methods in future studies may help address discrepancies in glutathione levels.

1. Introduction

Oxidative stress is defined as a build-up of damaging reactive oxygen species (ROS), and the inability of endogenous antioxidant defences to inactivate these species (Pizzino et al., 2017). When ROS accumulate to excess, they can cause damage to cellular components such as proteins, lipids, and nucleic acids (Sato et al., 2014). Neurons are particularly susceptible to the damaging effects of ROS due to the brain's large consumption of oxygen and reduced levels of protective antioxidant enzymes (Bošković et al., 2011). In patients with schizophrenia, studies have reported increased levels of ROS alongside a reduction in both peripheral and central antioxidants, such as glutathione (GSH) (Gunes et al., 2017; Wang et al., 2019; Kumar et al., 2020), while other reports have noted decreased levels of these antioxidants (Wood et al., 2009; Limongi et al., 2021). Possible causes of these disparate findings may be: substantial heterogeneity in patient profile, including stage of illness e.g. first episode psychosis compared to stable schizophrenia, or those with persistent chronic symptoms. Evidence suggests inflammation, relevant to oxidative stress, and/or glutamatergic function may differ by illness stage. (Murray et al., 2021; Upthegrove and Khandaker, 2019) An additional cause of contrasting findings includes substantial differences in acquisition methods and protocols adopted across studies (Wang et al., 2019; Rowland et al., 2016; Wijtenburg et al., 2017; Hafizi et al., 2018; Dempster et al., 2020).

Measurement of GSH in vivo is captured using magnetic resonance spectroscopy (MRS) acquisition. Due to its comparatively lower concentration relative to other metabolites such as glutamate or N-acetyl aspartate, reliable quantification of GSH presents additional technical

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challenges (Wilson et al., 2019). These include need for increased voxel size to improve the signal-to-noise ratio, more stringent requirements on magnetic field homogeneity and the use of metabolite specific acquisition methods to suppress unwanted overlapping metabolite signals (Mikkelsen and Hearshen, 2008). Given the length of acquisition and participant burden, decisions must also be made prior to data acquisition about what regions to focus on (i.e. voxel placement) and what pulse sequence to use (Tal et al., 2012). These additional challenges have subsequently caused large variations in study design that could be contributing to the disparate findings in the field.

Previous reviews of oxidative stress in schizophrenia have limited the region of interest to the anterior cingulate cortex (ACC) (Das et al., 2019), or the scanner strength to 7-Tesla (Sydnor and Roalf, 2020). To date no systematic review has examined clinical stage and demographic characteristics, or the additional effects of methodological variability. To address this evidence gap, we systematically review the current evidence base and present a quantitative *meta*-analysis of existing MRS studies examining GSH in schizophrenia spectrum psychoses. By consolidating results across a number of studies and assessing how different illness stages, acquisition methodologies and confounds may affect results, this *meta*-analysis aims to give a definitive answer as to whether GSH is reduced in schizophrenia and provide insight into the methodological improvements that may improve consistency in ongoing research, increasing the potential for mechanistic and pharmacological interventions for schizophrenia in the future.

2. Methods

2.1. Article Search

The systematic review was registered with PROSPERO under ID 42021226634. Relevant articles were extracted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al., 2021) (see Fig. 1 and Supplementary materials). Systematic searches of the literature were performed in the following databases: PubMed, PsycINFO, Web of Science, MEDLINE, and Embase up to July 23rd, 2023. The search terms used were as follows:

A. Schizo* OR psychosis OR first episode schizo* OR first episode psychosis OR high-risk for schizo* OR high-risk for psychosis OR prodrome

AND

B. Oxidative stress OR oxidative defen* OR antioxid* defen* OR Glutathione OR GSH.

AND

C. Magnetic resonance spectroscopy OR 1H-MRS OR MRS.

Additionally, a manual search was conducted within the reference lists of review articles and full-text articles that met the eligibility criteria for this analysis. A supplementary search using Google Scholar was also performed to identify articles not indexed in the aforementioned databases. The systematic search was carried out by AM, and both AM and CH independently assessed articles for inclusion and exclusion criteria.

2.2. Inclusion and exclusion Criteria

Articles written in English, either full-length or short, were included in the review if they met the following criteria: (1) The study was conducted in a cohort of individuals diagnosed with schizophrenia, first-episode psychosis, schizoaffective disorder, or clinical high-risk for psychosis; (2) The study included a healthy control comparison group;

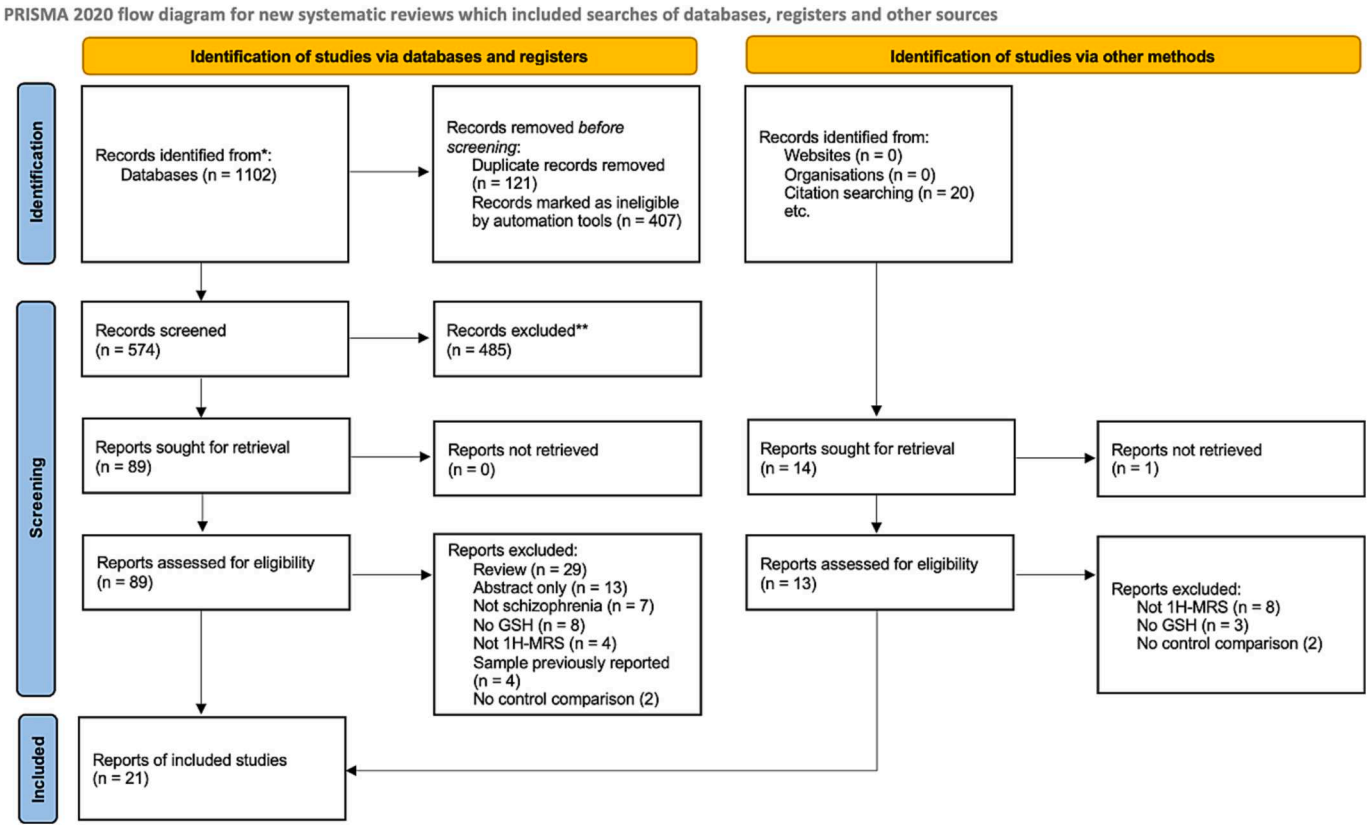

Fig. 1. PRISMA Flow Diagram Highlighting the Literature Search Process.

(3) Glutathione levels were measured using 1H-MRS; (4) Sufficient data were provided or could be obtained to calculate standardized mean differences between the groups. Studies reporting glutathione levels measured with chemical shift imaging or 13C-MRS were excluded, as well as studies where the patient sample completely overlapped. Studies that did not meet the criteria for the *meta*-analysis but fulfilled the original search terms were still included in the narrative synthesis.

The quality assessment of individual studies was conducted using a modified version of the checklist introduced by Das et al. (2019). This checklist was employed to evaluate both the methodology utilized in magnetic resonance spectroscopy (MRS) acquisition and analysis, as well as the overall quality of study demographics and reporting. The modifications to the checklist were based on the "Minimum Reporting Standards for in vivo Magnetic Resonance Spectroscopy (MRSinMRS): Experts' consensus recommendations" proposed by Lin et al. (2021).

By employing this assessment, each study was rated on a scale from 0 to 18, providing an indication of the potential reliability of the reported results. Supplementary Table 1 provides the details of the modified checklist used for the quality evaluation of the individual studies. If a study scored below 75 % on the data quality measures, then it was excluded from the analysis. Further analysis was conducted to assess if study quality could explain any of the variance seen in the primary *meta*-analysis.

2.3. Data Extraction

Studies included in this review involved in vivo measurement of GSH using 1H-MRS in individuals with a clinical diagnosis of a schizophrenia

Table 1
Characteristics of studies included in this review.

Author	Sample (PSY/HC)	PSY Type	% on Antipsychotics	Mean Age (PSY)	Mean Age (HC)	PSY % Male	HC % Male	ROIs	Field Strength (t)	MRS Sequence	Echo Time (ms)	Quality Score
(Brandt et al., 2016)	48 (24/24)	SZ	100.00	37.50	36.60	83.33	79.17	ACC	7	STEAM	28.00	18
(Coughlin et al., 2020)	26 (16/10)	SZ	86.96	34.20	32.10	73.91	68.00	ACC	3	MEGA-PRESS	35.00	17
(Da Silva et al., 2018)	56 (30/26)	CHR	13.33	20.30	22.80	50.00	38.46	mPFC	3	MEGA-PRESS	68.00	17
(Do et al., 2000)	28 (14/14)	SZ	35.71	32.20	35.60	100.00	100.00	mPFC	1.5	PRESS	75.00	15
(Girgis et al., 2019)	39 (19/20)	SZ	73.68	38.20	37.60	73.68	70.00	ACC	3	PRESS	68.00	18
(Godlewska et al., 2021)	34 (16/18)	FEP	88.23	25.69	27.10	100.00	100.00	ACC DLPFC Put	7	STEAM	11.00	17
(Hafizi et al., 2018)	28 (27/21)	CHR	0.00	20.30	22.86	51.85	47.62	mPFC	3	MEGA-PRESS	68.00	17
(Iwata et al., 2021)	92 (67/25)	SZ	100.00	43.71	40.80	75.13	73.08	ACC	3	MEGA-PRESS	68.00	17
(Kumar et al., 2020)	72 (27/45)	SZ	100.00	27.18	27.89	71.43	64.44	ACC InsulaVC	7	STEAM	17.00	18
(Lesh et al., 2019)	70 (33/37)	FEP	N/A	21.40	21.90	69.44	67.50	DLPFCVC	3	MEGA-PRESS	131.00	18
(MacKinley et al., 2022)	87 (57/30)	FEP	52.60	22.75	21.57	84.21	63.33	ACC	7	Semi-LASER	70.00	17
(Matsuzawa et al., 2008)	36 (16/20)	SZ	100.00	30.70	30.00	60.00	75.00	mPFC	3	MEGA-PRESS	94.00	16
(Ravanfar et al., 2022)	26 (12/14)	SZ	100.00	36.20	32.60	58.33	42.86	ACC	7	STEAM	6.00	18
(Reid et al., 2019)	42 (21/21)	FEP	95.24	23.20	23.50	76.19	76.19	ACC	7	STEAM	5.00	18
(Rowland et al., 2016)(a)	56 (27/29)	SZ	81.48	34.40	29.70	62.96	48.28	ACC	7	STEAM	14.00	18
(Rowland et al., 2016)(b)	98 (45/53)	SZ	91.10	37.70	37.10	64.40	60.38	ACC	3	STEAM	6.50	18
(Taylor et al., 2017)	34 (16/18)	SZ	87.50	22.70	23.90	81.25	61.11	ACCThal	7	STEAM	10.00	18
(Terpstra et al., 2005)	22 (13/9)	SZ	100.00	26.00	25.00	61.53	44.44	ACC	4	STEAM	5.00	14
(Wang et al., 2019)	162 (74/88)	FEP	N/A	22.30	23.30	70.37	46.15	ACC CSO DLPFC OFRThal	7	STEAM	14.00	18
(Wijtenburg et al., 2017) (Old)	86 (47/39)	SZ	91.67	49.50	51.20	55.32	64.10	mPFC	3	STEAM	6.50	18
(Wijtenburg et al., 2017) (Young)	99 (48/51)	SZ	95.74	25.20	25.20	70.83	46.30	mPFC	3	STEAM	6.50	18
(Xin et al., 2016)	58 (25/33)	FEP	80.00	24.80	25.40	72.00	54.55	mPFC	3	SPECIAL	6.00	18

PSY Type abbreviations: SZ – schizophrenia, CHR – clinical high risk, FEP – first episode psychosis.
ROIs abbreviations: ROI – region of interest, ACC – anterior cingulate cortex, mPFC – medial prefrontal cortex, VC – visual cortex, DLPFC – dorsolateral prefrontal cortex, Thal – thalamus, CSO – centrum semiovale, OFR – orbitofrontal region, Put - putamen.
MRS Sequence abbreviations: STEAM - stimulated echo acquisition mode, MEGA-PRESS - Mescher-Garwood point resolved spectroscopy, semi-LASER - semi-localized by adiabatic selective refocusing, SPECIAL - spin-echo full-intensity acquired localized spectroscopy.

spectrum disorder (including first episode and/or stable cases) or individuals at clinical high-risk for psychosis. Data extracted from each study included mean and standard deviation of GSH levels for both the patient and control groups, along with various demographic and methodological variables (see Table 1). In instances where group-specific mean and standard deviation values were not reported, authors were contacted twice over the course of one month. Risk of bias was assessed by AM using Egger's test and leave-one-out analysis was used to assess study weighting.

2.4. Analysis

The *meta*-analysis was performed using the metafor package (version 4.2) (Viechtbauer, 2010) in R (version 4.3.0) (R Core Team, 2023). GSH concentration differences between psychosis patients and healthy controls were standardized using Hedge's g effect sizes. Hedge's g accounts for potential bias in small sample sizes, providing a more robust and reliable estimation of the treatment effect. It is calculated as the difference between the two raw mean scores divided by the pooled standard deviation, adjusted by sample size.

Initially, separate *meta*-analyses were conducted to assess GSH levels in specific brain regions. However, for further subgroup and *meta*-regression analysis, studies where the voxel was placed in the medial-prefrontal cortex (mPFC), or ACC were combined into a single group. These regions were selected due to their substantial overlap and the large number of studies reporting GSH levels in these areas.

Subgroup analyses were performed based on the phase of illness, including stable schizophrenia (symptoms present for more than 2 years, stably medicated), first episode psychosis (within 2 years of symptom onset, minimally medicated), and clinical high-risk. Additionally, further groupings were based on magnetic field strength and MRS pulse sequence. In the subgroup analysis, Cramer-Rao lower bounds (CRLB) were also assessed, using a cut-off of < 20 %. However, *meta*-regressions could not be conducted on CRLB data due to the limited number of studies reporting raw CRLB statistics.

For the *meta*-regressions, various factors were assessed to determine their effect on the results. These factors included age, sex, medication status, sample size, symptom severity, echo time, and voxel size. To ensure standardized scores across different symptom measures, the percentage of maximum possible symptom scores (POMP) was calculated. This standardization method allows for comparisons across scoring methods, overcoming the issues associated with alternative standardization approaches (e.g., z-scores) that do not facilitate comparisons of scores across studies and samples. The use of POMP ensures that symptom scores are in a standardized format for analysis (Cohen et al., 1999).

3. Results

3.1. Search Results

We identified 21 case-control studies with a healthy control (HC) comparison group, providing group-specific mean and standard deviation values for *meta*-analysis (Wang et al., 2019; Kumar et al., 2020; Rowland et al., 2016; Wijtenburg et al., 2017; Hafizi et al., 2018; Brandt et al., 2016; Coughlin et al., 2020; Do et al., 2000; Girgis et al., 2019; Iwata et al., 2021; Lesh et al., 2019; Matsuzawa et al., 2008; Ravanfar et al., 2022; Rowland et al., 2016; Taylor et al., 2017; Terpstra et al., 2005; Godlewska et al., 2021; MacKinley et al., 2022; Reid et al., 2019; Xin et al., 2016; Da Silva et al., 2018). Additionally, one study (Wijtenburg et al., 2017) presented comparisons across two patient-control groups – old and young schizophrenia, with age-matched controls. In this case, both comparisons were included as separate data points since there was no overlap between the groups. All studies were published between December 2001 and October 2022. Two additional studies (Reyes-Madrigal et al., 2019; Wood et al., 2009) met the inclusion criteria; however, these studies used unique voxel locations (caudate and temporal lobe, respectively), preventing *meta*-comparisons.

This *meta*-analysis included data from 672 psychosis patients and 641 healthy controls. The psychosis group's age ranged from 19.4 to 49.5 years (M = 30.18, SD = 8.27), comprising 70.43 % male participants, with 60.72 % medicated with anti-psychotics. Among the studies, 14 involved participants with stable schizophrenia/schizoaffective disorder (i.e. stably medicated with an illness duration > 2.5 years) (Kumar et al., 2020; Rowland et al., 2016; Wijtenburg et al., 2017; Brandt et al., 2016; Coughlin et al., 2020; Do et al., 2000; Girgis et al., 2019; Iwata et al., 2021; Lesh et al., 2019; Matsuzawa et al., 2008; Ravanfar et al., 2022; Rowland et al., 2016; Taylor et al., 2017; Terpstra et al., 2005), while 5 studies (224 SZ, 227 HC) were conducted in individuals experiencing first-episode psychosis (i.e., within 2 years of symptom onset) (Wang et al., 2019; Godlewska et al., 2021; MacKinley et al., 2022; Reid et al., 2019; Xin et al., 2016). Only 2 studies included a clinical high-risk sample (Hafizi et al., 2018; Da Silva et al., 2018). Five studies reported concentrations across multiple voxels (Wang et al., 2019; Kumar et al., 2020; Lesh et al., 2019; Taylor et al., 2017; Godlewska et al., 2021), and one study had two eligible contrasts (Wijtenburg et al., 2017), resulting in a total of 28 datasets. For the initial analysis, studies were separated by voxel location (ACC, mPFC, DLPFC, etc.). Subsequent analysis focused solely on a combined grouping of the ACC and mPFC voxels, termed "medial frontal" (Merritt et al., 2021) to avoid including assessments of the same participant cohorts multiple times.

3.2. Meta-Analyses

14 studies positioned the voxel in the ACC, 6 in the mPFC, 3 in the DLPFC, 2 in the thalamus, and 2 in the VC. The application of random effects analysis revealed no significant difference in GSH levels between patients with psychosis and healthy controls in any of these investigated brain regions (see Fig. 2).

Voxel placement in either the mPFC or ACC was observed in 20 out of 21 studies, encompassing a total of 639 patients and 704 controls. These studies were combined into a group labelled "medial frontal" voxels [42]. Once more, the analysis demonstrated no significant difference in GSH levels between patients and controls within this grouping (k = 21, d = -0.09, CI = -0.28 to 0.10, p = 0.37).

3.3. Subgroup Analysis

Subgroup analysis showed a significant reduction in GSH levels among individuals with stable schizophrenia (constituting 58 % of the sample) (k = 14, d = -0.20, CI = -0.40 to −0.00, p = 0.05). However, this was not replicated in the FEP subgroup (34 % of the sample) (k = 5, d = 0.15, CI = -0.40 to 0.70, p = 0.59) or the clinical high-risk subgroup (8 % of the sample) (k = 2, d = 0.14, CI = -0.25 to 0.53, p = 0.47). Heterogeneity was notable in both the FEP and stable schizophrenia subgroups ($Tau^2 = 0.32$, $Chi^2 = 20.65$, df = 4, $p < 0.001$, $I^2 = 84$ %; $Tau^2 = 0.06$, $Chi^2 = 24.47$, df = 13, p = 0.03, $I^2 = 42$ % respectively). Fig. 3.

Furthermore, no significant alterations in GSH levels were observed in patients compared to controls when studies were stratified by magnetic field strength: 3 T (k = 10, d = -0.12, CI = -0.29 to 0.05, p = 0.39) or 7 T (k = 9, d = 0.09, CI = -0.28 to 0.45, p = 0.64). Additionally, when grouped by pulse sequence, no specific sequence yielded significant results. Notably, only one study reported utilizing the semi-LASER sequence, and within this study, GSH levels were found to be significantly higher in FEP compared to HC. Studies who report a CRLB cutoff of < 20 % also demonstrated no difference in GSH levels (k = 16, d = -0.05, CI = -0.27 to 0.16, p = 0.63).

3.4. Meta-Regression Analysis

No statistically significant moderator effects were found across the whole PSY group for patient age (Z = -0.86p = 0.39), proportion of

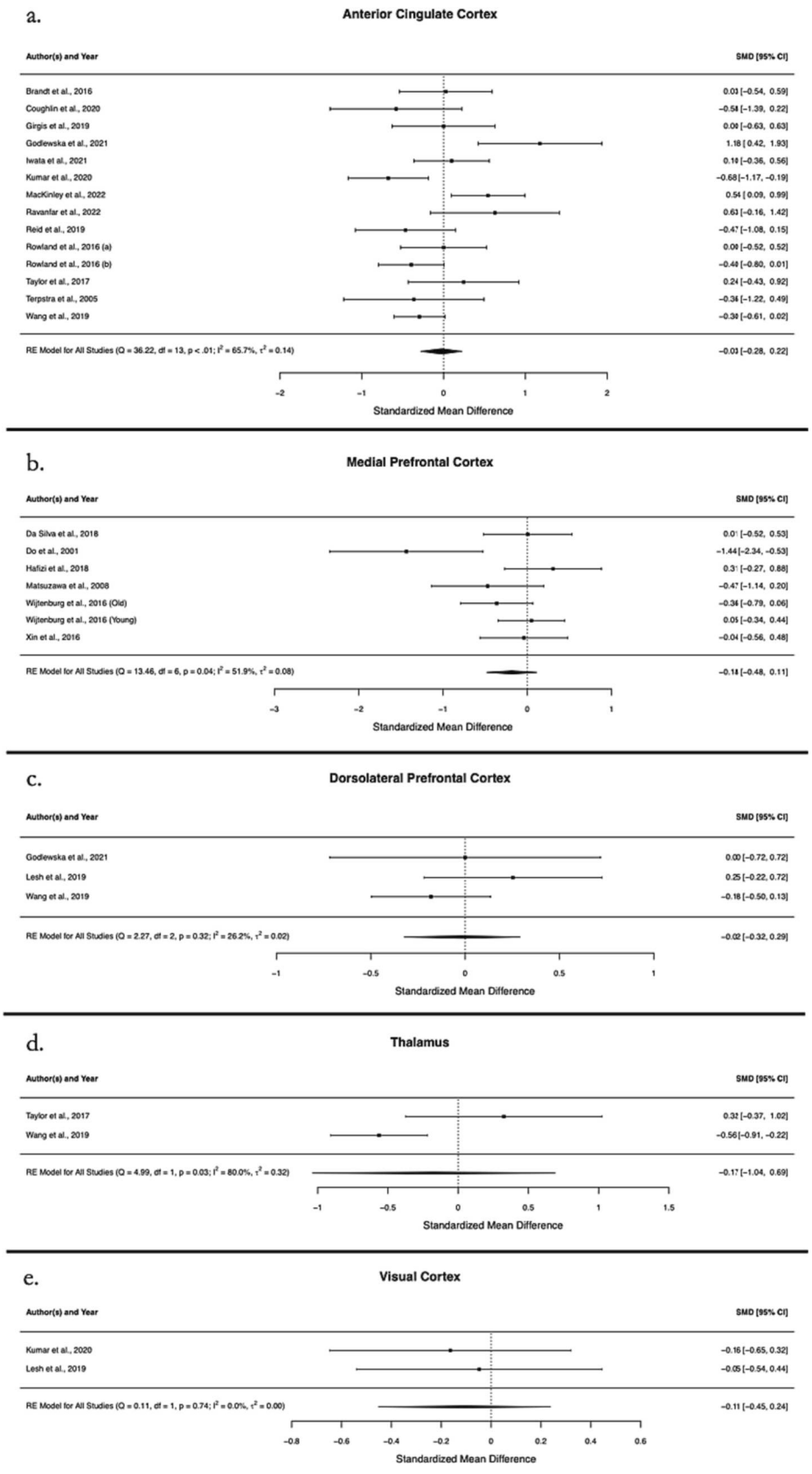

Fig. 2. Forest Plot of Standard Mean Difference in GSH Between PSY and HC Groups in Different Voxel Locations.

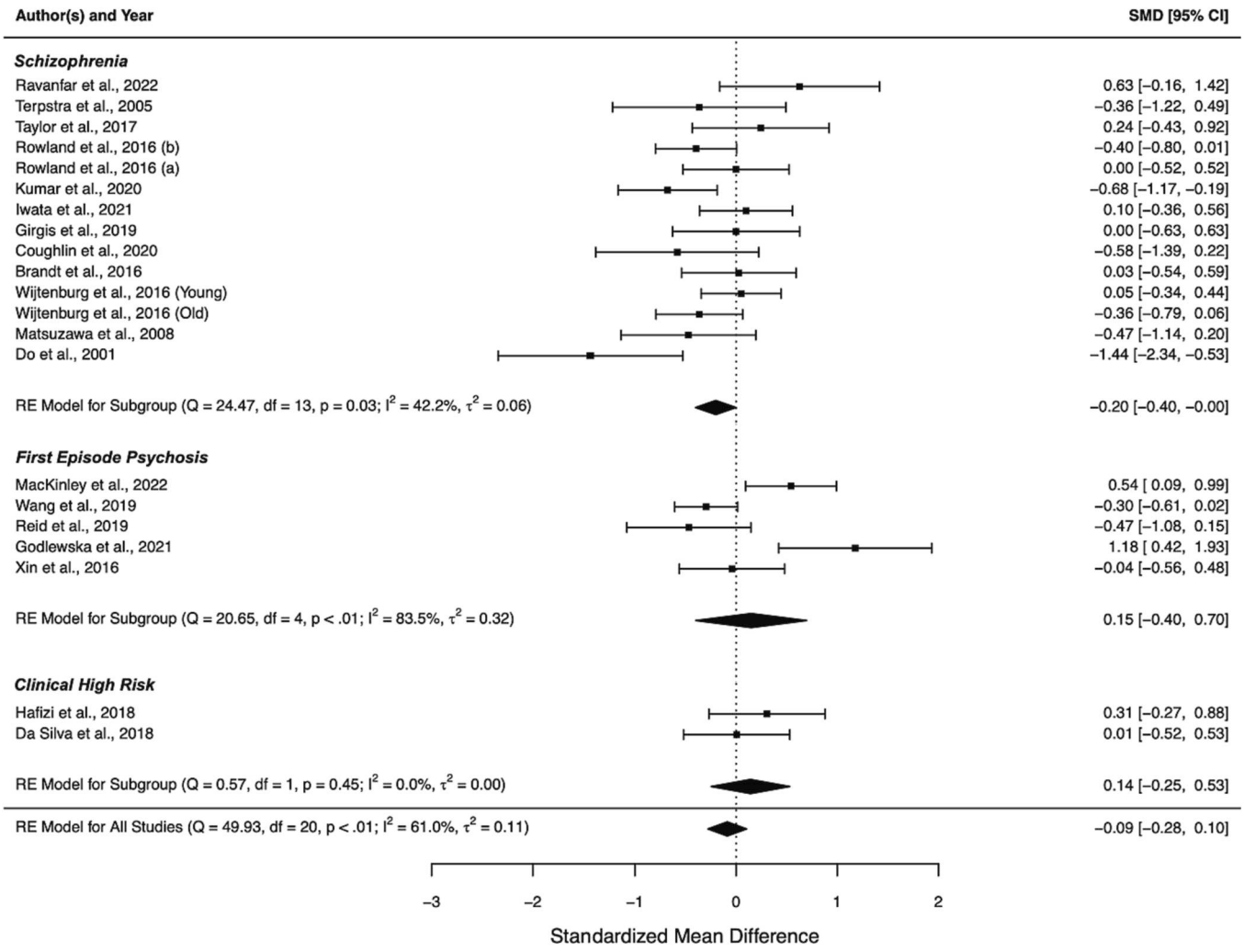

Fig. 3. Forest Plot of Standard Mean Difference in GSH Between PSY and HC Grouped by Illness Phase.

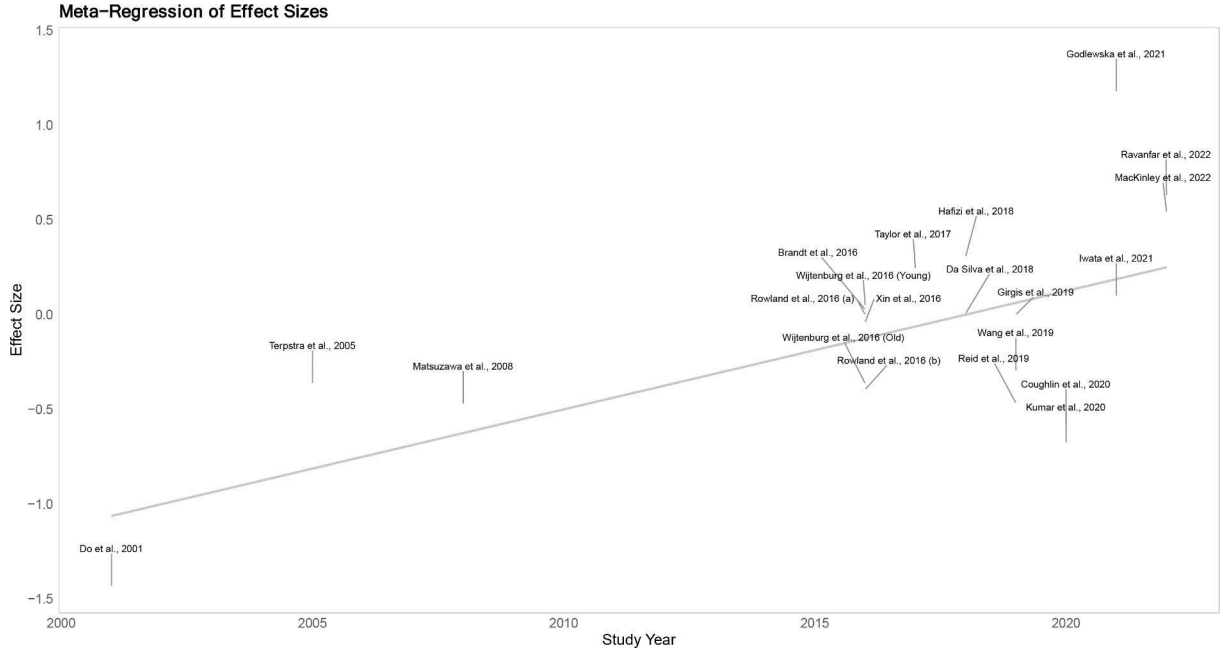

Fig. 4. Meta-Regression of Year of Study Effect on Effect Sizes.

medicated patients (Z = -0.78, p = 0.44) or patient gender (Z = 0.50, p = 0.62). Furthermore, no significant effects of methodological moderators were found such as echo time (Z = -0.02, p = 0.98), voxel size (Z = -0.73, p = 0.47), and sample size (Z = -1.29, p = 0.20), or study quality score (Z = -0.01, p = 0.94). Regression analyses did not find a significant association of GSH with negative symptoms (Z = -0.55, p = 0.58) or positive symptoms (Z = -0.59, p = 0.56). These results persisted when looking at either the FEP or the stable schizophrenia subgroups.

There was, however, a significant association with study year – with older studies demonstrating a greater GSH reduction than their more recent counterparts (Z = 3.04, p < 0.01). This was also demonstrated in the stable schizophrenia subgroup (Z = 2.29, p = 0.02), but not the FEP subgroup (Z = 1.32, p = 0.19). Fig. 4.

3.5. Risk of Bias

Inspection of funnel plots indicated no clear evidence of publication bias in the "medial frontal" group (Fig. 5). Egger's test was not significant (T = 0.33, p = 0.74) indicating that results were likely representative of the field. This finding was replicated in both the FEP and stable schizophrenia subgroups (T = 1.12, p = 0.34; T = -0.44, p = 0.66 respectively). All iterations of leave one out (LOO) analysis, resulted in consistent findings.

LOO sensitivity analysis within the stable schizophrenia grouping showed that the removal of any one of seven separate studies (Kumar et al., 2020; Wijtenburg et al., 2017; Coughlin et al., 2020; Do et al., 2000; Matsuzawa et al., 2008; Rowland et al., 2016; Terpstra et al., 2005) would result in a non-significant finding, with Rosenberg's fail-safe N indicating 11 non-significant studies would need to be included to give an overall non-significant finding (see supplement).

4. Discussion

The current study represents the largest *meta*-analysis of in vivo central GSH levels within patients with psychosis to date. Our findings reveal a significant reduction in GSH among patients with stable schizophrenia but not in patients with broader defined psychosis, those with first episode or clinical high-risk, when compared to healthy controls. In the *meta*-regression analysis, we found that symptom severity, demographic factors, and MRS methods did not significantly influence the effect sizes. However, a significant association between the year of study and the extent of GSH reductions within the psychosis group was found. Specifically, older studies demonstrated greater reductions in GSH compared to more recent studies. This effect was also evident in the stable schizophrenia subgroup, suggesting that it is not solely due to an increase in FEP-focused studies over time. Assessment of publication bias indicated that the data included in this analysis are likely representative of the field.

Our findings of no significant reduction in GSH across all clinical stages of psychosis is consistent with a number of studies (Wijtenburg et al., 2017; Coughlin et al., 2020; Matsuzawa et al., 2008). However, these findings run counter to two recent *meta*-analyses of schizophrenia which demonstrate significant reductions in GSH in the ACC region and in studies at 7 T respectively (Das et al., 2019; Sydnor and Roalf, 2020). Evidence for a reduction of GSH converges from a variety of study designs, including post-mortem, genetic, animal and clinical trials (Gawryluk et al., 2011; Michels et al., 2018; Steullet et al., 2017; Hashimoto, 2019). Our differing results could also be due to the inclusion of MRS studies across all clinical stages of psychosis, reflecting an increase in heterogeneity. Inconsistency of 1H-MRS studies has been suggested to result from a lack of a "gold standard" acquisition method (Fisher et al., 2020); however, we note that no significant methodological variables had a moderating effect. Inconsistency of results may be indicative of a specific subgroup of patients who have reduction in GSH; those with or on a path to stable schizophrenia.

It has previously been suggested that this subgroup may represent up to one third of patients and is characterised by very low levels of polyunsaturated fatty acids within red blood cells during the acute phase of illness, signifying persistent redox dysregulation (Bentsen et al., 2011; Solberg et al., 2019). Furthermore, those with a specific glutamate cysteine ligase catalytic (GCLC) subunit polymorphism may have lower levels of GSH in the brain, thus suggesting there may be a genetic component to this subgroup (Xin et al., 2016). It may be that GSH reductions are not present in the early stage of is indicative of the substantial heterogeneity within the FEP population, indeed we found that heterogeneity was much higher in the FEP cohort than the stable cohort. First episode patients who present with significant GSH reductions may be predisposed to progress to more persistent illnesses.

To our knowledge this is the first *meta*-analysis to demonstrate that GSH reductions may be limited to patients with stable schizophrenia regardless of other clinical and demographic variables. It has been proposed that the abnormalities in GSH levels may arise due to damage

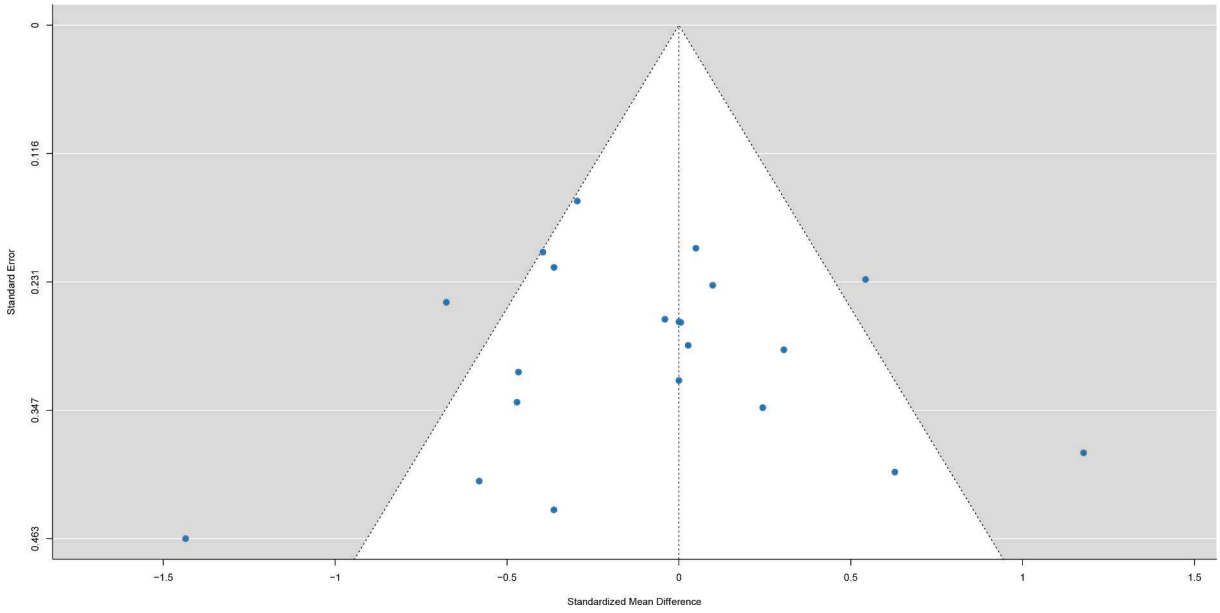

Fig. 5. Funnel Plot of All "Medial Frontal" Studies.

caused by glutamatergic hyperactivity in the early phase of the disorder (Kumar et al., 2020). As such in first episode patients GSH levels may be similar to those seen in healthy controls or slightly increased to compensate for the excess ROS generated by the ongoing damage (Limongi et al., 2021). Furthermore, an increase in GSH in the early phase of illness is associated with more favourable long-term outcomes (Wijtenburg et al., 2017), and thus a greater number of first episode patients who may be part of the oxidative stress vulnerable subgroup would progress to an established phase of the disorder.

This finding could be influenced by the inclusion of older studies. We demonstrate a significant interaction between the year of study and differences in GSH levels between patients and controls. The three studies conducted before 2008 (Do et al., 2000; Matsuzawa et al., 2008; Terpstra et al., 2005) had notably lower GSH levels in stable schizophrenia compared to healthy controls. The removal of any one of these three studies led to the overall finding falling below the significance threshold. This relationship might be attributed to advancements in MRS methodologies, more stringent reporting criteria, and technological improvements in brain imaging. Older studies likely employed less sophisticated techniques, resulting in reduced accuracy and greater variation in reported GSH findings. Moreover, researchers have become more diligent in ensuring consistency and accuracy of data collection and analysis, with a focus on improving data quality (Lin et al., 2021). While we found no association with methodologies, other unmeasured or unaccounted factors could also be contributing to this observation.

The present study has several strengths including a large sample, the largest to-date to our knowledge, with little influence of publication bias. However, some limitations need to be considered. Firstly, the data did not allow for control of additional confounding factors such smoking, BMI and food intake. Studies have demonstrated that these can influence GSH levels (Manna and Jain, 2015; Young et al., 2007; Zhang et al., 2007).

Secondly, the combined group of mPFC and ACC may have been too diverse. It has been noted that glutamatergic alterations may be more apparent in the rostral area of the ACC compared to the dorsal area (Jeon et al., 2021). A large medial frontal grouping of voxels would be unable to detect these small changes in metabolite concentrations across neighbouring regions.

Thirdly, it has been noted that both schizophrenia and antipsychotics can affect the relaxation rates of metabolites (Bracken et al., 2013), therefore it is likely that MRS acquisition methods and medication status will affect the ability to detect changes in concentration between PSY and HC, however we found no confounding influence of medication exposure in our analysis. Whilst we included several acquisition variables in our *meta*-regression, given the small number of studies within certain subgroups we suggest cautious interpretation of these analyses.

While several studies reported CRLB cutoffs below 20 %, the most widely used cutoff for GSH quantification (Kreis, 2015), only two studies provided raw CRLB scores (Ravanfar et al., 2022; Reid et al., 2019). The absence of raw CRLB scores from multiple studies limited our ability to comprehensively evaluate the impact of data quality on the quantification of GSH levels in our *meta*-analysis. Poor data quality could potentially lead to differential effects on the accurate determination of GSH concentrations, affecting the reliability of the results across studies, as has been demonstrated for glutamate (Smucny et al., 2021) and NAA and choline (Yang et al., 2023).

Despite the significant advances in MRS acquisition and analysis in recent years, alongside a significant effort by the research community to unify reporting criteria (Lin et al., 2021), comparing across studies remains challenging as researchers have not settled on a best practice for metabolite quantification. For GSH quantification, a J-edited pulse sequence, with longer echo times (~130 ms) for higher editing efficiency (Nezhad et al., 2017) is recommended. While some authors have noted that this may not offer advantages over other common methods e.g. STEAM or PRESS (Ravanfar et al., 2022; Duffy et al., 2014), these methods may overestimate GSH levels, particularly in concentrations less than 3 mM (Wijtenburg et al., 2014), furthermore, these studies represent the "gold standard" of PRESS acquisition, reporting the use of short echo times and experienced MRS operators. This is not always reflective of the field as typically longer echo times are employed for PRESS acquisition as GSH is rarely the metabolite of interest. To combat the potential deleterious effects of the inclusion of these 3 T press studies a sensitivity analysis was conducted with these studies removed. The results of which can be found in the Supplementary materials (Supplementary Figure S5).

Furthermore, methods of metabolite reporting frequently change from study to study, Hoch et al. (2017) suggested that reporting metabolite ratios e.g. GSH: creatine, offers multiple advantages compared to raw metabolite levels such as reduced sample size and an increase in statistical significance. MRS studies in schizophrenia will often report metabolite levels in relation to creatine, in these cases creatine is used as a reference point as it is assumed that creatine levels will not vary across subgroups. Some studies have demonstrated significant alterations in creatine levels in the DLPFC and ACC in schizophrenia (Wood et al., 2003; Öngür et al., 2009) however two separate *meta*-analyses found no significant differences between schizophrenia and healthy controls (Yang et al., 2023; Kraguljac et al., 2012). Additionally, if the researcher is employing a J-edited pulse sequence, which is recommended, a second sequence will also be required to acquire spectra for the reference metabolite.

Although progress has been achieved in improving Magnetic Resonance Spectroscopy (MRS) techniques and establishing consistent reporting methods, the varying ways studies are conducted alongside challenges in accurately measuring metabolite levels highlight the intricate nature of understanding and contrasting results in MRS-related research. It is essential to carefully acknowledge these methodological intricacies to ensure the strength and accuracy of MRS studies when examining conditions such as schizophrenia.

This *meta*-analysis indicates that reduced GSH and oxidative stress may be specific to people with stable schizophrenia, however, this may have been influenced by unmeasured variation in methodology – as demonstrated by the significant interaction with study year. Future work should focus on patient stratification and examining how GSH levels may differ between illness phases. From our *meta*-analysis, the results appear to be unaffected by variations in MRS acquisition, however further consistency is still warranted to improve individual study reporting and future pooling of data.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2023.09.017.

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