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Dynamic immune dysregulation in severe mental illness: Exaggerated innate and attenuated adaptive immune responses following SARS-CoV-2 vaccination

Tim Rietberg^{a,b}, Kawtar El Abdellati^{a,b}, Alexandre Lucas^c, Margot Lemarinier^c, Steven Fried^c, Jean-Romain Richard^d, Ryad Tamouza^d, Violette Coppens^{a,b}, Manuel Morrens^{a,b}, Marion Leboyer^d, Livia De Picker^{a,b,*} 

^a Collaborative Antwerp Psychiatric Research Institute (CAPRI), University of Antwerp, Antwerp, Belgium

^b Scientific Initiative of Neuropsychiatric and Psychopharmacological Studies (SINAPS), University Psychiatric Centre Duffel, Duffel, Belgium

^c University Toulouse, Institut des Maladies Métaboliques et Cardiovasculaires (I2MC), INSERM, We-Met Platform, UMR 1297-I2MC, Toulouse, France

^d INSERM U955 IMRB, Translational Neuropsychiatry Laboratory, AP-HP, Hôpital Henri Mondor, DMU IMPACT, Fédération Hospitalo-Universitaire de Médecine de Précision en Psychiatrie (FHU ADAPT), Paris Est Créteil University, Fondation FondaMental, Créteil, 94010, France

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ABSTRACT

Background: Immune dysregulation in severe mental illness (SMI) is usually characterised using static measurements. As such, how the immune system of SMI patients responds to real-world challenges remains largely unknown. Prior studies suggest that patients may exhibit an exaggerated innate and attenuated adaptive immune response, but in vivo studies are lacking.

Objectives: This study aimed to assess immune responses to SARS-CoV-2 vaccination in SMI patients compared to non-psychiatric controls (NPCs). We investigated post-vaccination changes in cytokine and antibody levels, their associations, and secondary measures including tryptophan-kynurenine pathway metabolites and psychiatric symptoms.

Methods: We collected blood samples of 72 SMI patients and 127 NPCs before and after the first and second vaccine dose administrations to quantify cytokines (IL1 β , IL6, IL8, IL10) and anti-SARS-CoV-2 antibodies (Spike, S1, S2, S1RBD, Nucleocapsid). We used linear mixed models to assess whether post-vaccination changes in biomarker levels differ between SMI patients and NPCs, and to evaluate associations among biomarkers.

Results: SMI patients showed significantly greater increases in IL1 β (F(394.3) = 30.03, $P_{FDR} < 0.001$) and IL8 (F(384.4) = 15.28, $P_{FDR} = 0.005$) levels following the first vaccine dose and smaller increases in Spike (F(508.7) = 8.58, $P_{FDR} = 0.005$), S1 (F(506.9) = 19.76, $P_{FDR} < 0.0001$) and S2 (F(507.8) = 20.96, $P_{FDR} < 0.0001$) antibody levels after two vaccine doses when compared to NPCs. Higher cytokine levels were associated with lower antibody response in SMI patients.

Conclusion: Our findings provide in vivo evidence for exaggerated innate and attenuated adaptive immune responses to vaccination in SMI patients. The study underscores the need for longitudinal, experimental approaches in immunopsychiatry to better characterise the dynamic dysregulation of both the innate and the adaptive immune system in this population.

Abbreviations: AUC, area under the curve; ACE2, angiotensin-converting enzyme 2; BPRS, Brief Psychiatric Rating Scale; ELISA, enzyme-linked immunosorbent assay; HRP, horseradish peroxidase; IL, interleukin; KYN, kynurenine; KYNA, kynurenic acid; LLOQ, lower limit of quantification; mRNA, messenger RNA; NPC, non-psychiatric controls; PANSS, Positive and Negative Syndrome Scale; QUINO, quinolinic acid; RBD, receptor-binding domain; SMI, severe mental illness; TNF α , tumor necrosis factor alpha; TRYCAT, tryptophan catabolite; TRP, tryptophan; ULOQ, upper limit of quantification.

* Corresponding author. Collaborative Antwerp Psychiatric Research Institute (CAPRI), University of Antwerp, Antwerp, Belgium.

E-mail address: livia.depicker@uantwerpen.be (L. De Picker).

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1. Introduction

The immune system's functionality is defined by its dynamic response to challenges, such as infection or vaccination, and yet immune dysregulation in severe mental illness (SMI; including psychotic and major mood disorders) has traditionally been characterised using static measurements, emphasizing chronic abnormalities. As a result, much less is known about how the innate and adaptive immune systems of SMI patients respond to real-world immunological challenges.

The innate immune system comprises various cell types that coordinate the primary immune response, using cytokines to communicate. Key proinflammatory cytokines such as interleukin (IL) 1 β , IL6, IL8 and tumour necrosis factor alpha (TNF α) activate downstream immune components, including T- and B-cells of the adaptive immune system (Watkins et al., 1995). Together, T- and B-cells provide robust, flexible defences and immune memory through antibody production (Kang and Compans, 2009). Proinflammatory cytokines also promote tryptophan (TRP) metabolism along the kynurenine (KYN) pathway (KP), a crucial immunoregulatory system that helps meet increased energy demands and resolve inflammation (Seo and Kwon, 2023), while producing several neuro-active metabolites such as kynurenic- (KYNA) and quinolinic acid (QUINO) (Badawy, 2017; Schwarcz and Stone, 2017).

Dysregulations of these systems are well-documented in SMI patients. Meta-analyses show elevated levels of circulating proinflammatory cytokines (Goldsmith et al., 2016; Zhang et al., 2023), indicative of chronic innate immune hyperactivity, alongside decreased peripheral TRP and KYN levels, an increased KYN:TRP ratio and diagnosis- or state-specific deviances further down the KP (Hebbrecht et al., 2021; Marx et al., 2021; Morrens et al., 2020). Similarly, SMI patients show increased neutrophil to lymphocyte ratios (NLR) and B-cell counts, as well as altered distributions of both T- and B lymphocyte subsets (Clausen et al., 2024; Sørensen et al., 2023; van Mierlo et al., 2019; Wu et al., 2024).

In contrast, how these systems respond to an immune challenge remains relatively understudied in this population. Christian et al. (2010) and Glaser et al. (2003) both report that depressive symptoms predict exaggerated innate inflammatory responses to the influenza vaccine, but these studies were respectively conducted in samples of otherwise healthy pregnant women or older adults and measured only a single cytokine. These findings do however converge with in-vitro work in SMI patients. For instance, Costi et al. (2021) found that lipopolysaccharide (LPS) stimulation resulted in a higher release of inflammatory factors from isolated peripheral blood mononuclear cells (PBMCs) of 30 unmedicated major depressive disorder (MDD) patients compared to non-psychiatric controls (NPCs), while Vogelzangs et al. (2016) reported an association between depression, as well as the severity of symptoms, and the level of inflammatory markers after whole blood LPS stimulation in a sample of 1242 MDD patients. Similarly, Kozłowska et al. (2019) found that cytokine production by mitogen-stimulated PBMCs of schizophrenic patients was three-fold higher than NPCs. These findings suggest that SMI patients may exhibit an exaggerated innate response to immune challenges, but as of yet no studies have been conducted in vivo to address this possibility.

The adaptive immune response, on the other hand, has garnered a little more attention during the recent COVID pandemic. Kaneko and Tsuboi (2023) found that depressive symptoms predict attenuated antibody response to the SARS-CoV-2 vaccine, with lower antibody responses also observed in schizophrenia (Nemani et al., 2024) and psychotic disorders (O'Brien et al., 2024) compared to NPCs. This suggests that an attenuated adaptive immune response following real-world immunological challenges may be a transdiagnostic feature of SMI, but further investigation is needed to confirm this hypothesis.

Overall, while immune dysregulation is increasingly acknowledged in SMI pathophysiology, there is a striking lack of data assessing the immune response to real-world challenges. Focusing on dynamic responses rather than static measurements can provide a deeper

understanding and better characterization of immune function and dysregulation in SMI.

The present study thus employs vaccination as an immune challenge to examine dynamic immune responses in a longitudinal transdiagnostic cohort of SMI patients compared to NPCs. The primary research questions are whether post-vaccination changes in cytokine and antibody levels differ between SMI patients and NPCs. We hypothesised that SMI patients would exhibit exaggerated innate and attenuated adaptive immune responses following vaccination. Additionally, associations between cytokine and antibody levels are examined. Secondary objectives include evaluating post-vaccination changes in TRP and KP metabolite levels and examining associations between immune markers and psychiatric symptoms.

2. Methods and materials

2.1. Study design and participants

In this longitudinal case-control study, adult SMI patients and age-matched non-psychiatric controls (NPCs) without prior COVID-19 infection and who were scheduled to receive their first SARS-CoV-2 vaccination dose, were enrolled at two study sites in Belgium and France respectively. Blood samples were prospectively collected immediately prior to- and after the first vaccine dose administration, as well as before and after the second (i.e. booster) dose administration.

2.1.1. Belgian cohorts

Between February 22, 2021 and July 13, 2021, patients with chronic SMI were recruited at the University Psychiatric Centre Duffel (UPC Duffel) in Flanders as part of a larger multi-centre study (see El Abdellati et al., 2023 for a full description of this cohort). All eligible patients registered for vaccination at UPC Duffel were invited to participate, resulting in the inclusion of 36 patients who received BioNTech/Pfizer (BNT162b2), Moderna (mRNA-1273), or AstraZeneca (AZD1222) SARS-CoV-2 vaccines. An additional cohort of 127 age-matched NPCs was recruited from hospital staff working at UPC Duffel.

Vaccines were administered according to national clinical protocols, which followed the approved dosing and recommended intervals for each vaccine (Pfizer: 21 days; Moderna: 28 days; AstraZeneca: 4–12 weeks). In practice, strict adherence to these intervals proved challenging, particularly for the SMI group. This resulted in some extended follow-up periods, with a maximum of 170 days from first vaccine dose to final sample, compared to 108 days for the NPCs. For this reason, time was included as a continuous variable in statistical analyses.

Blood samples were collected through venipuncture at (1) baseline, immediately prior to the first vaccine dose; (2) approximately 7 days after the first dose (intended timing, actual mean: 7.8 days, SD: 12.26); (3) immediately prior to the second dose; and (4) approximately 21 days after the second dose (mean: 21.02, SD: 2.75). Plasma and serum were extracted by standard protocol, aliquoted and stored at -80°C . Sampling around day 7 post-first dose was chosen to capture early innate and emerging adaptive immune responses, whereas post-second dose sampling was timed to align with the expected peak of the adaptive immune response. These time points are consistent with standard vaccine immunogenicity research protocols.

COVID-19 infection history was assessed using participant reports, hospital PCR test records, and centralised medical records. Exclusion criteria for all participants included a known history of COVID-19 infection or vaccination and inability or unwillingness to provide consent.

The study was approved by the Ethics Committees of the University Hospital Antwerp and Emmaus, with all participants providing written informed consent.

2.1.2. French patient cohort

Using the same protocol as the Belgian cohort, 36 additional SMI

patients were enrolled at Assistance Publique-Hôpitaux de Paris (AP-HP). Participants at this site all received BioNTech/Pfizer vaccines. The study was approved by the Comité de Protection des Personnes Sud Est V and all participants provided written informed consent.

2.2. Outcomes

2.2.1. Innate immune response

We quantified serum levels of IL1 β , IL6, IL8 and IL10 in triplicate using the automated immunoassay platform, Ella (ProteinSimple/Bio-Techne, CA, USA) with the Simple Plex Cytokine Storm Panel (Ref. # ST01A-PS-003229). Concentrations in pg/mL were calculated by the instrument software (Simple Plex Explorer, ProteinSimple/Bio-Techne, CA, USA). We replaced values below or above the manufacturer-provided lower or upper limits of quantification (LLOQ or ULOQ) with LLOQ/2 and ULOQ+1, respectively. The LLOQ and ULOQ of each cytokine, the percentage of samples that fell between them and the coefficient of variation of these samples are reported in [Supplementary Table 1](#).

2.2.2. Adaptive immune response

We quantified Anti-SARS-CoV-2 antibodies in serum samples using Simple Western technology (Jess, ProteinSimple/Bio-Techne, CA, USA) with the SARS-CoV-2 Multi-Antigen Serology Module. This automated capillary-based system enables size electrophoretic sorting and immunolabeling. We used a mixture of his-tagged recombinant SARS-CoV-2 proteins (Spike, S1 Subunit, S2 Subunit, S1 Receptor-Binding Domain (RBD), Nucleocapsid) to detect specific antibodies. The Spike protein is a key target of the immune response and vaccination, as it mediates viral entry into host cells. The S1 and S2 subunits are components of the Spike protein: S1 contains the RBD, which directly interacts with the angiotensin-converting enzyme (ACE)2 receptor on human cells, while S2 is involved in membrane fusion and viral entry. These proteins are critical indicators of vaccine-induced immunity. In contrast, the Nucleocapsid protein, which encapsulates the viral RNA, is not included as an outcome measure because it is typically not targeted by vaccines, but is useful for detecting prior natural infection (Magazine et al., 2024). It was therefore used in the construction of a 'latent prior exposure variable', described below. By quantifying antibodies to the Spike protein as well as its subunits, we aimed to comprehensively capture the adaptive immune response to vaccination. This approach allows for a more fine-grained assessment and may reveal subtle differences in the quality of the immune response between groups.

We mixed these proteins with fluorescent master mix, heated the mixture to 95 °C for 5 min, diluted serum samples 1:10 in serum diluent (ProteinSimple; SA-001) for IgG detection and used Anti-human IgG-HRP (ProteinSimple 043-491, ready-to-use) for immunodetection. We dispensed denatured proteins, blocking reagent, washing buffer, antibodies, and chemiluminescent substrate into a microplate, and loaded samples in duplicate into a 25-capillary cartridge (12–230 kDa separation matrix). Protein separation and immunodetection were performed automatically using default settings. We used Compass Software to measure the area under the curve (AUC) of electropherogram peaks corresponding to the immunodetection of each protein. We excluded samples with low signal-to-noise ratios and used remaining AUC values in subsequent analyses.

Despite exclusion criteria based on known history of COVID-19 infection, some participants showed elevated antibody levels at baseline. This could indicate cross-reactivity with other, similar virus strains, yet may also be the result of unknown prior exposure to COVID-19. We thus used the AUC values of antibodies to the Spike protein and its subunits, as well as antibodies to the Nucleocapsid protein, to construct a binary variable post-hoc, with a cut-off Total AUC $>1.2 \times 10^6$ indicating latent prior exposure to COVID-19 (in line with the method previously described by [El Abdellati et al., 2023](#)). This prior exposure variable was included in sensitivity analysis for all primary models to

test the robustness of the findings in both exposed and non-exposed individuals. All results remained unchanged unless reported otherwise.

2.2.3. Secondary measures

TRYCATS. In the Belgian cohorts, we quantified plasma levels of TRP and its catabolites KYN, KYNA, and QUINO (TRYCATS) using competitive enzyme-linked immunosorbent assays (ELISAs). We grouped plasma samples by patient ID and randomly distributed them in single across ELISA plates, each containing two control samples with known concentrations and six standard solutions. We performed ELISAs according to the manufacturer's protocol to obtain optical density (OD) measures and fitted a four-parameter polynomial curve to the OD output of the six standard solutions to approximate the concentration of each metabolite. We standardised OD values as a proportion of the plate-specific maximum OD, corresponding to the lowest concentration (B/b0 values). To avoid perpetuating noise generated by polynomial approximation, we used these standardised values in further processing steps. We reduced plate-dependent variance by extracting residuals from an ANOVA fitted to the B/b0 values with plate number as predictor. We then inverted these residuals to appropriately reflect directionality in subsequent analyses.

Psychiatric Symptoms. In the Belgian patient cohort only, we assessed psychiatric symptomatology using the Brief Psychiatric Rating Scale (BPRS) and the 6-item Positive and Negative Syndrome Scale (PANSS-6). The BPRS consists of 18 items rated on a 7-point Likert scale (1 = not present to 7 = extremely severe), covering a broad range of psychiatric symptoms including anxiety, depression, and psychosis. The PANSS-6 is a brief version of the original 30-item PANSS and includes six core items: three assessing positive symptoms (P1, P2, P3) and three negative symptoms (N1, N4, N6), each rated from 1 (absent) to 7 (extreme). We calculated sum scores for both scales, as well as PANSS Positive and Negative scores from the respective subscales.

2.3. Statistical analysis

2.3.1. Pre-processing and descriptive statistics

To address differential immune responses following administration of vector vs. mRNA vaccines ([Nam et al., 2022](#)), we created a new variable "Vaccine Type" grouping Pfizer and Moderna as mRNA vaccines and contrasting them with AstraZeneca's vector vaccine. This distinction was also used to mitigate confounding from the uneven distribution of vaccine brands across cohorts and study sites, which arose due to local vaccination policies ([Supplementary Table 2](#)). We winsorised biomarker data at the 95th percentile to mitigate the influence of outliers and log-transformed non-normally distributed variables prior to analysis. We grouped P-values per research question and corrected for multiple comparisons using the Benjamini-Hochberg False Discovery Rate (P_{FDR}), with a threshold of < 0.05 .

We calculated descriptive statistics including percentages, means and standard deviations to describe the study population. We used chi-square tests and t-tests to examine relationships between diagnostic groups and covariates. All processing steps and analyses were conducted using R 4.3.1 and JMP Pro 16 respectively.

2.3.2. Innate and adaptive immune responses

To assess whether post-vaccination changes in cytokine and antibody levels differ between SMI patients and NPCs, we employed linear mixed models including age, BMI, and Vaccine Type as covariates, with Participant ID as a random factor nested within Country (Belgium/France). Time was included as a continuous measure indicating the number of days since vaccination.

We initially conducted analyses across all four assessments, thus including both vaccine dose administrations. Subsequently, we ran two separate models for each vaccine administration, using "Days since First Vaccine" (assessments 1, 2 and 3) and "Days since Second Vaccine" (assessments 3 and 4) as the Time variable. We were primarily interested

in interaction terms Time * Group(SMI/NPC), except in the overarching models for cytokine levels, which we used to assess trait-level differences between the two groups. We then included Sex(Female/Male) and the interaction term Sex * Time in each model. If the latter was significant, we repeated analyses for males and females separately, incorporating all other covariates.

2.3.3. Associations between innate and adaptive responses

To assess associations between cytokine levels and antibody response, we first fitted linear mixed models separately for each of the four antibodies (Spike, S1, S2 and S1RBD), using time, cytokines, and their interactions as predictors. We then included any cytokine that significantly influenced antibody levels in a new model, together with the Cytokine * Time interaction term, which was of primary interest, and all other covariates. We then ran these models separately for SMI patients and NPCs to evaluate group differences. Since changes in biomarker levels and group differences were most evident following the first vaccine dose administration, only that first assessment period was included in this analysis.

2.3.4. Secondary research questions

We analysed TRP and KP metabolite levels using the same method as for cytokines and antibodies. Following visual inspection of the data, we conducted additional exploratory post-hoc analyses including only the first 10 days following the first vaccine dose administration.

We examined associations between biomarkers and psychiatric symptoms in the Belgian patient cohort. Using the procedure described in Section 2.5.3, (sub)scores of the PANSS and BPRS were used as outcome measures, with cytokines or KP metabolites as predictors.

3. Results

We included a total of 72 SMI patients and 127 NPCs, of which some were to lost follow-up just prior to or following the second vaccine administration. Among the SMI group, 58 patients completed at least three assessments, and 42 completed all four. See [Supplementary Table 3](#) for the number of available datapoints per analysis and [Supplementary Table 4](#) for a comparison between patients who participated up until the final assessment and those who did not. Notably, patients who dropped out had significantly higher baseline levels of cytokines and antibodies. To address potential bias introduced by this differential drop-out, we conducted sensitivity analyses restricted to participants who completed the final assessment when applicable.

Of the total SMI patient group, 48 had a schizophrenia spectrum disorder, the rest had major mood disorders. Out of 72 patients, 18 used anti-depressants, 27 used anti-psychotics (mean daily chlorpromazine equivalent dose 179.87 mg) and 12 used sedatives (mean daily diazepam equivalent dose 3.28 mg). No patients used lithium or anti-epileptics. Controlling for medication use did not meaningfully alter the results of any primary analyses.

The SMI patient group had a significantly higher proportion of male participants, a higher mean BMI and a higher number of active smokers. Moreover, they had significantly higher levels of all cytokines and antibodies at baseline. Over 75 % of participants received mRNA vaccines. See [Table 1](#) for an overview of these statistics.

3.1. Innate immune system

3.1.1. Overall cytokine levels

We expected SMI patients to demonstrate trait-level elevated cytokine concentrations (see [Supplementary Table 5](#) for concentrations). Irrespective of time, levels of IL1 β (F(df) = 85(174.4), $P_{FDR} < 0.0001$), IL6 (F(172.9) = 104.48, $P_{FDR} < 0.0001$), IL8 (F(173.2) = 68.02, $P_{FDR} < 0.0001$) and TNF α (F(172.5) = 83.51, $P_{FDR} < 0.0001$) were indeed significantly higher in SMI patients than NPCs after adjusting for covariates. See [Table 2](#) and [Supplementary Table 6](#).

Table 1
Demographics.

	SMI (72)	NPC (127)	<i>p</i>	SMD
Females [n(%)]	24 (33.33)	106 (83.46)	<0.001	1.18
Age [mean(SD)]	44.26 (13.86)	46.48 (10.99)	0.250	-0.18
BMI [mean(SD)]	28.32 (6.05)	25.60 (4.80)	0.002	0.50
Smokers [n(%)]	42 (68.85)	15 (11.90)	<0.001	-1.43
Vaccine Type				
mRNA[n(%)]	62 (86.11)	97 (76.38)	0.140	-0.25
Vector[n(%)]	10 (13.89)	30 (23.62)		
Cytokines at baseline				
IL1 β [mean(SD)]	0.42 (0.62)	0.12 (0.12)	0.001	0.66
IL6 [mean(SD)]	5.86 (6.51)	2.17 (1.30)	<0.001	0.79
IL8 [mean(SD)]	66.62 (135.28)	13.51 (4.30)	0.001	0.56
TNF α [mean(SD)]	20.25 (14.30)	11.24 (2.40)	<0.001	0.88
Antibodies at baseline				
Spike [mean(SD)]	4.82 (5.24)	0.56 (0.66)	<0.001	1.14
S1 [mean(SD)]	4.29 (5.04)	0.22 (0.29)	<0.001	1.14
S2 [mean(SD)]	3.22 (3.55)	0.27 (0.42)	<0.001	1.17
S1RBD [mean(SD)]	5.68 (6.82)	0.29 (0.47)	<0.001	1.12
Nucleocapsid [mean(SD)]	2.81 (3.92)	0.23 (0.33)	<0.001	0.93

Note. *P*-values calculated by χ^2 and *t*-test for categorical and continuous data respectively. Cytokines in pg/ml. Antibody levels represented by the area under the receiver operator curve (AUC), divided by factor 10e5 for legibility.

3.1.2. Innate immune responses following the first vaccine dose administration

Following the first vaccine, IL1 β (F(394.3) = 30.03, $P_{FDR} < 0.001$) and IL8 (F(384.4) = 9.16, $P_{FDR} = 0.005$) levels increased significantly more in SMI patients compared to NPCs after adjusting for covariates ([Fig. 1](#)). For IL8 this interaction was significant in females (F(257.7) = 30.95, $P_{FDR} < 0.001$) but not males (F(125.5) = 1.5, $P_{FDR} = 0.28$) ([Supplementary Table 8](#)). IL6 and TNF α levels did not significantly change following vaccination in either group, regardless of sex. See [Table 2](#) and [Supplementary Table 7](#).

3.1.3. Innate immune responses following the second vaccine dose administration

Following the second vaccine dose administration, IL1 β and IL8 decreased significantly, with IL1 β decreasing significantly less in SMI patients compared to NPCs (F(147.4) = 21.07, $P_{FDR} < 0.0001$). Again, IL6 and TNF α did not change in either group. See [Table 2](#) and [Supplementary Table 9](#).

3.2. Adaptive immune system

3.2.1. Adaptive immune response following both vaccine dose administrations

SARS-CoV-2 Spike antibodies as well as antibodies to the S1 and S2 sub-units and S1RBD increased over time, spanning both vaccine dose administrations. mRNA vaccines yielded significantly higher Spike (F(218.7) = 100.56, $P_{FDR} < 0.0001$), S1 (F(221.4) = 50.41, $P_{FDR} < 0.0001$) and S2 (F(222.6) = 50.75, $P_{FDR} < 0.0001$) antibody levels.

SMI patients showed significantly attenuated increases of antibody levels to Spike (F(508.7) = 24.09, $P_{FDR} < 0.001$), S1 (F(506.9) = 19.76, $P_{FDR} < 0.0001$) and S2 (F(507.8) = 20.96, $P_{FDR} < 0.0001$) proteins over time when compared to NPCs ([Fig. 2](#)). For Spike antibody, this interaction was significant for males (F(160.3) = 5.04, $P_{FDR} = 0.04$) but not females (F(335.7) = 1.59, $P_{FDR} = 0.19$) ([Supplementary Table 11](#)). S1RBD levels did not differ between groups. See [Table 3](#) and [Supplementary Table 10](#).

These group differences remained significant in sensitivity analyses restricted to participants who participated up until the final assessment, indicating that the observed attenuation is not attributable to differential drop-out.

Table 2
Cytokine levels following the first, second or both vaccine dose administrations.

Cytokine (Log[pg/ml])	Both Vaccine Doses Included		First Vaccine Dose Only		Second Vaccine Dose Only	
	β (95 % CI)	F Ratio	β (95 % CI)	F Ratio	β (95 % CI)	F Ratio
IL1β						
Group[SMI]	0.57(0.45; 0.69)	85.0***	0.55(0.43; 0.67)	86.6***	0.65(0.49; 0.81)	64.57***
Time[Days]	0.002(0.001; 0.004)	7.49**	0.004(0.002; 0.007)	15.16***	-0.01(-0.014; -0.005)	19.34***
Group * Time	0.003(0.002; 0.005)	19.51***	0.006(0.004; 0.008)	30.03***	-0.01(-0.014; -0.006)	21.07***
IL6						
Group[SMI]	0.39(0.31; 0.46)	104.48***	0.38(0.30; 0.47)	81.84***	0.41(0.31; 0.52)	65.33***
Time[Days]	0.003(0.001; 0.004)	13.39***	0.005(0.003; 0.007)	18.67***	-0.005(-0.012; 0.003)	1.49
Group * Time	0.001(0.00; 0.003)	2.22	0.002(0.00; 0.004)	3.73 \dagger	-0.002(-0.009; 0.006)	0.17
IL8						
Group[SMI]	0.46(0.35; 0.58)	68.02***	0.44(0.33; 0.55)	61.22***	0.49(0.35; 0.64)	43.65***
Time[Days]	0.003(0.001; 0.004)	15.97***	0.005(0.003; 0.007)	20.37***	-0.006(-0.01; -0.001)	6.73*
Group * Time	0.002(0.001; 0.004)	12.18***	0.003(0.001; 0.005)	9.16**	-0.001(-0.006; 0.003)	0.3
TNFα						
Group[SMI]	0.19(0.15; 0.23)	83.51***	0.19(0.15; 0.24)	75.65***	0.16(0.11; 0.22)	33.33***
Time[Days]	0.00(-0.001; 0)	0.56	0.001(0; 0.002)	1.27	-0.002(-0.004; 0.00)	2.33
Group * Time	0.00(-0.001; 0.001)	0.01	0(-0.001; 0.001)	0.37	0(-0.002; 0.002)	0.02

Note. * $p \leq .05$; ** $p \leq .01$; *** $p \leq .001$; $\dagger p \leq .1$. Covariates were included but not shown in table, see supplementary materials for full results. 'First Vaccine Dose Only' includes assessments 1, 2 and 3; 'Second Vaccine Dose Only' includes assessments 3 and 4.

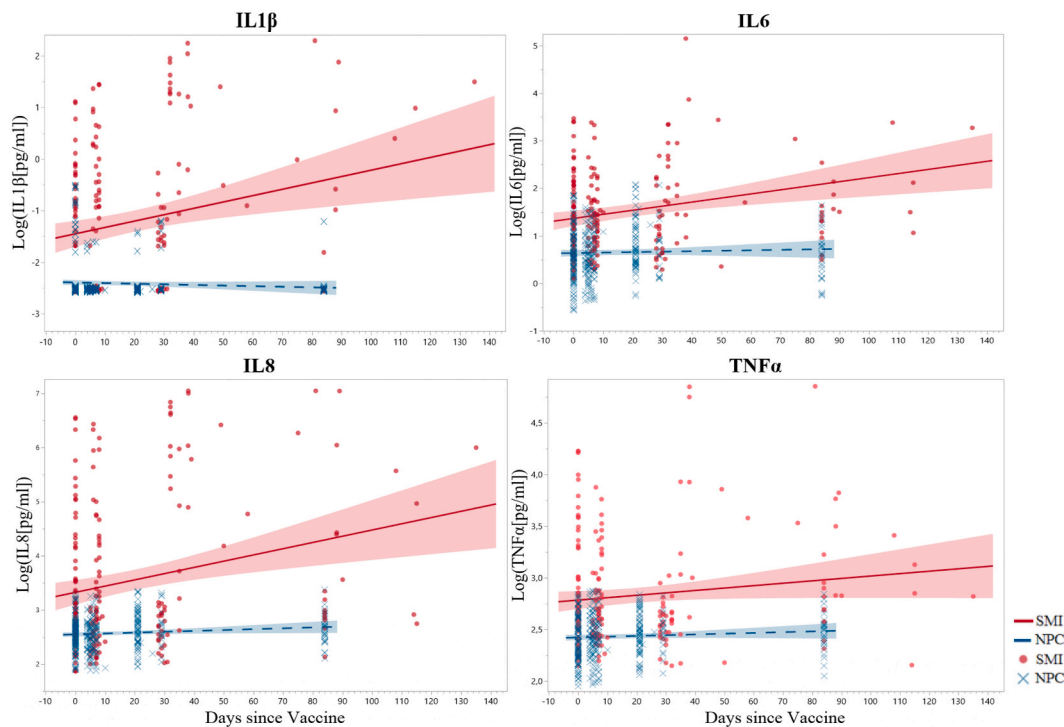


Fig. 1. Cytokine levels following the first vaccine dose, administered at day 0 immediately following sample collection. IL1 β ($F(394.3) = 30.03$, $P_{FDR} < 0.001$) and IL8 ($F(384.4) = 9.16$, $P_{FDR} = 0.005$) levels increased significantly more in SMI patients compared to NPCs after adjusting for covariates.

3.2.2. Adaptive immune responses following the first vaccine dose administration

Following the first vaccine dose administration, SMI patients showed significantly attenuated increases of Spike ($F(337.4) = 11.95$, $P_{FDR} = 0.002$), S1 ($F(315.7) = 4.57$, $P_{FDR} = 0.02$) and S2 ($F(328.8) = 6.98$, $P_{FDR} = 0.04$) antibodies after adjusting for covariates. S1RBD levels did not differ between groups. See [Table 3](#) and [Supplementary Table 12](#).

There was a significant Sex*Time interaction effect for Spike ($F(df$

$= 5.22(323.8)$, $P = .023$) and in this model, the Group*Time interaction was no longer significant, nor was it in the separate models for males and females. See [Supplementary Table 13](#).

3.2.3. Adaptive immune responses following the second dose administration

Antibody levels for Spike, S1, S2 and S1RBD antibodies did not differ between groups following the second vaccine dose administration. See [Table 3](#) and [Supplementary Table 14](#).

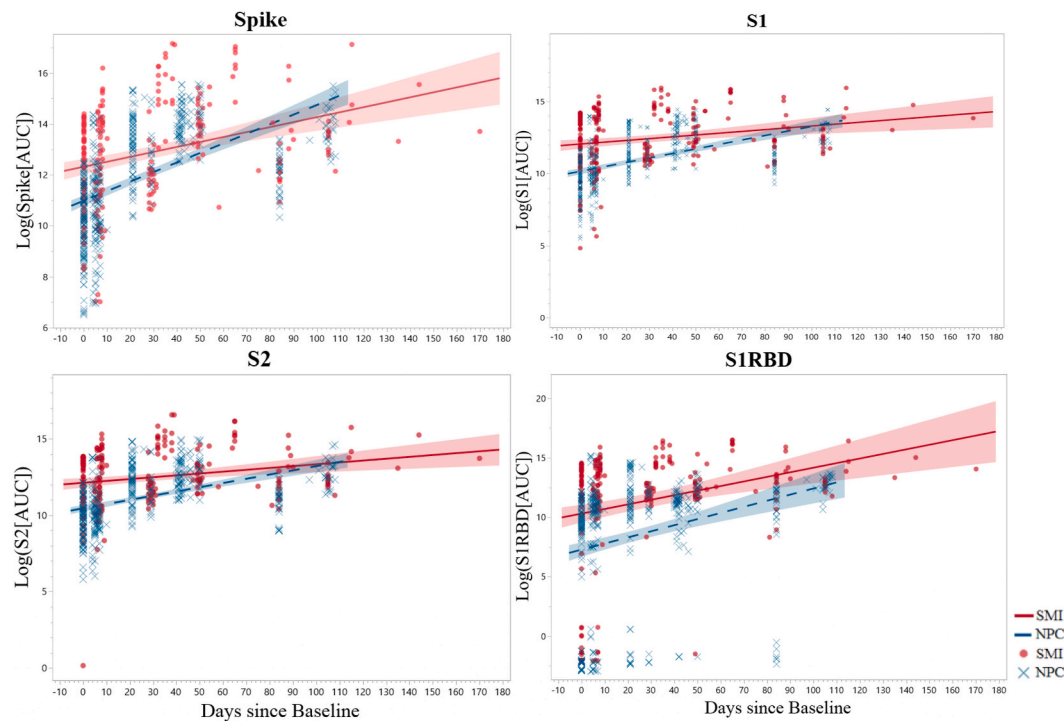


Fig. 2. Antibody levels following two vaccine dose administrations. The first was administered at day 0, immediately following sample collection. The second vaccine was administered between 28 and 135 days since baseline for the SMI group (mean: 47.67 days, SD: 28.84) and between 21 and 84 days for the NPC group (mean: 37.32, SD: 26.36), depending on differing guidelines across vaccine types and variable adherence in practice. SMI patients showed significantly attenuated increases of antibody levels to Spike ($F(508.7) = 24.09, P_{FDR} < 0.001$), S1 ($F(506.9) = 19.76, P_{FDR} < 0.0001$) and S2 ($F(507.8) = 20.96, P_{FDR} < 0.0001$).

Table 3
Antibody levels following vaccine dose administrations.

Antibody (Log[AUC])	Both Vaccine Doses Included		First Vaccine Dose Only		Second Vaccine Dose Only	
	β (95 % CI)	F Ratio	β (95 % CI)	F Ratio	β (95 % CI)	F Ratio
Spike						
Group[SMI]	0.11(-0.06; 0.28)	1.74	0.30(0.09; 0.50)	8.16**	0.11(-0.07; 0.29)	1.47
Time[Days]	0.04(0.036; 0.045)	344.19***	0.03(0.028; 0.041)	101.31***	0.06(0.05; 0.07)	126.47***
Group * Time	-0.01(-0.01; -0.006)	24.09***	-0.01(-0.02;-0.005)	11.95***	0.01(-0.004; 0.02)	1.17
S1						
Group[SMI]	0.40(0.22; 0.58)	19.69***	0.61(0.39; 0.83)	29.43***	0.34(0.15; 0.52)	13.07***
Time[Days]	0.03(0.028; 0.036)	224.33***	0.02(0.018; 0.031)	57.09***	0.05(0.04; 0.06)	81.62***
Group * Time	-0.01(-0.01; -0.005)	19.76***	-0.007(-0.01;-0.001)	4.57*	-0.01(-0.02; 0.004)	1.49
S2						
Group[SMI]	0.35(0.19; 0.51)	17.75***	0.57(0.31; 0.77)	32.46***	0.24(0.04; 0.43)	5.87*
Time[Days]	0.03(0.024; 0.032)	176.88***	0.02(0.016; 0.029)	47.15***	0.03(0.02; 0.04)	37.41***
Group * Time	-0.01(-0.01; -0.005)	20.96***	-0.01(-0.02; -0.002)	6.98**	-0.004(-0.01; 0.00)	0.53
S1RBD						
Group[SMI]	1.19(0.72; 1.66)	24.86***	1.37(0.79; 1.95)	21.94***	0.34(0.15; 0.52)	13.07***
Time[Days]	0.04(0.025; 0.048)	38.45***	0.03(0.01; 0.05)	8.2**	0.05(0.04; 0.06)	81.62***
Group * Time	-0.008(-0.02; 0.003)	2.06	-0.001(-0.02; 0.02)	0.01	-0.01(-0.02; 0.00)	1.49

Note. * $p \leq .05$; ** $p \leq .01$; *** $p \leq .001$; $\dagger p \leq .1$. Covariates were included but not shown in table, see supplementary materials for full results. 'First Vaccine Dose Only' includes assessments 1, 2 and 3; 'Second Vaccine Dose Only' includes assessments 3 and 4.

3.3. Associations between innate and adaptive vaccine responses

Following the first vaccine dose administration, increased IL1 β was significantly associated with attenuated increases in Spike ($F(362.2) = 21.41, P_{FDR} < 0.0001$), S1 ($F(356) = 26.24, P_{FDR} < 0.0001$), S2 ($F(347.1) = 25.59, P_{FDR} < 0.0001$) and S1RBD ($F(362.5) = 5.12, P_{FDR} = 0.02$) antibody levels. Increased IL8 was significantly associated with

attenuated Spike antibody levels ($F(376) = 20.44, P_{FDR} < 0.0001$), as was increased TNF α with attenuated S1 ($F(322.2) = 20.44, P_{FDR} < 0.0001$) and S2 ($F(346.7) = 19.75, P_{FDR} < 0.0001$) antibody levels.

All of these effects were specific to SMI patients and not apparent in NPCs. See [Supplementary Tables 15–21](#).

3.4. Secondary research questions

3.4.1. TRYCAT levels after vaccine administration

There were no differences in TRYCAT levels between groups (see [Supplementary Table 2](#) for mean concentrations) and no significant changes in either group overall, nor after the first or second vaccine dose administration. Visual inspection ([Supplementary Fig. 1](#)) prompted a post-hoc exploration of only the first 10 days following the first vaccine dose administration, which revealed a significant increase in KYN ($F(158.7) = 6.31, P_{FDR} = 0.04$) and KYNA ($F(162.7) = 5.31, P_{FDR} = 0.04$) in both groups.

3.4.2. Associations between immune markers and psychiatric symptoms

Psychiatric symptom scores decreased slightly over time, although not significantly. Symptom scores were not associated with any biomarker. In the post-hoc exploration of the first 10 days following the first vaccine dose administration, KYNA was however significantly associated with lower BPRS sum scores ($F(37.0) = 7.80, p = .008$) overall and increases in KYNA correlated to a steeper decline of BPRS scores over time ($F(34.3) = 10.68, p = .003$).

4. Discussion

To our knowledge, this is the first study to longitudinally investigate dynamic responses to an immune challenge in both the innate and adaptive immune systems of SMI patients, and the largest study to date using an *in vivo* immune challenge in SMI patients. We hypothesised that SMI patients would have an exaggerated innate and an attenuated adaptive immune response following SARS-CoV-2 vaccination. Additionally, we explored the relationships between innate biomarkers, antibody responses and psychiatric symptoms.

4.1. Exaggerated innate immune response

On top of their already elevated cytokine levels at baseline, SMI patients showed greater increases in cytokine levels compared to NPCs following the first vaccine dose administration, which lasted up until administration of the second dose, up to 135 days later. These findings align with our expectations as well as prior *in vitro* work ([Costi et al., 2021](#); [Vogelzangs et al., 2016](#)) and studies on sub-clinical depressive symptoms predicting antibody response ([Christian et al., 2010](#); [Glaser et al., 2003](#)). They further corroborate the concept of ‘*trained innate immunity*’ as a mechanism in SMI pathophysiology ([Danese and J Lewis, 2017](#); [Salam et al., 2018](#)). Trained innate immunity is characterised by exaggerated responses to immune challenges, which may reflect epigenetic and metabolic reprogramming of innate immune cells due to early-life immunological or psychosocial stress ([Arneith, 2021](#)). No prior clinical studies have sought to confirm whether SMI patients indeed exhibit exaggerated innate immune responses to *in vivo* experimental and real-world immune challenges. This lack of immune-response data represents a blind spot in the field of immunopsychiatry, potentially overlooking critical factors that influence disease progression and quality of life for this vulnerable group. Our findings thus open the door to further exploration of this mechanism in SMI and its potential implications for treatment or prevention.

4.2. Attenuated adaptive immune response

As anticipated, SMI patients demonstrated attenuated increases in antibody levels against the SARS-CoV-2 Spike protein and its S1 and S2 subunits following two vaccine doses. When examining the two dose administrations in isolation, this difference was apparent after the first but not the second dose. Notably, antibody levels converged between groups following both vaccine dose administrations. However, SMI patients began with higher baseline antibody levels, potentially limiting further increase due to ceiling effects, which could partly explain the

attenuated overall increase observed. To address this, we included a binary prior exposure variable derived from the combined area under the curve (AUC) of all five antibody measures in all models. Additionally, we observed that patients who dropped out before completing all four assessments had significantly higher baseline antibody levels ([Supplementary Table 4](#)). To account for this potential bias, we conducted sensitivity analyses restricted to participants who participated up until the final assessment. Group differences remained significant after both adjustments, indicating that the attenuated responses in SMI patients are not solely driven by pre-existing immunity or differential drop-out and instead reflect altered vaccine-induced dynamics.

These findings align with previous studies showing that depressive symptoms predict reduced antibody responses ([Kaneko and Tsuboi, 2023](#)) and that individuals with schizophrenia ([Nemani et al., 2024](#)) or psychotic disorders ([O'Brien et al., 2024](#)) exhibit diminished vaccine responses. Notably, a subset of samples from the current study ($n = 21$ patients with schizophrenia vaccinated with mRNA vaccines) were included in the multicentre study of [Nemani et al. \(2024\)](#), but the antibody analyses have been conducted in a different laboratory using different methodology, assessing only the Spike protein. They reported attenuated response specifically after the second dose administration but not the first, a discrepancy that could be due to such differences in methodology and design (e.g. only including schizophrenia patients and mRNA vaccines, not excluding based on prior infection), or point towards a power issue in our analyses due to drop-out rates in the patient group around the second dose administration. Nevertheless, our results reinforce these earlier findings and generalise the attenuated post-vaccine adaptive immune responses to a broader group of SMI patients.

In contrast, [El Abdellati et al. \(2023\)](#) reported higher SARS-CoV-2 antibody levels in SMI patients compared to NPCs following natural infection, highlighting the need for further research to better understand underlying mechanisms. Such efforts should also aim to characterise vaccine responses on a more granular level. For example, we observed no group differences in antibody levels against the receptor-binding domain (RBD), despite significant differences for Spike and its S1 and S2 subunits. This selective pattern suggests that different functional components of the adaptive response may be differentially affected in SMI, emphasizing the value of multi-epitope approaches in future studies. In this regard, vaccination as an experimental model is especially well-suited because it allows for a more controlled environment than natural infection.

4.3. Associations between innate and adaptive immune responses

The observed attenuated adaptive vaccine response could stem from persistently elevated cytokine levels, which can desensitise various intracellular signalling pathways ([Alter and Sekaly, 2015](#); [Shen-Orr et al., 2016](#)), ultimately impairing T- and B-cell function and reducing antibody production. Consistent with this hypothesis, we found significant associations between inflammatory cytokines and lower antibody levels after the first vaccine dose in SMI patients but not in NPCs. Most notably, IL1 β showed a negative association with antibodies against the SARS-CoV-2 Spike protein and all its subunits, while TNF α was associated with reduced antibodies to the S1 and S2 subunits, and IL8 specifically impacted anti-Spike antibodies.

Impaired vaccine responses are well-documented in the context of immunosenescence, a phenomenon characterised by elevated proinflammatory cytokines and reduced adaptive immune responses. Interestingly, immune dysregulation in SMI patients closely resembles these features. It has been proposed that systemically dampening inflammation prior to vaccination or employing targeted anti-inflammatory adjuvants such as cytokine blockers may enhance vaccine efficacy in the elderly ([Alter and Sekaly, 2015](#); [Pereira et al., 2020](#)), an orthogonal approach to traditional proinflammatory vaccine adjuvants. A similar approach could potentially also benefit SMI patients by improving their

immune response to vaccination, but this needs to be investigated in clinical trials.

4.4. Limitations and future directions

Due to the naturalistic design of this study some demographic and clinical characteristics were unequally distributed between the SMI and NPC groups. Notably, only 33 % of SMI patients were female, opposed to 83 % of NPCs. To account for this difference, we have included sex as covariate in all analyses, and ran additional sex-split analyses where needed. Our analyses suggest that certain observed effects may be sex-specific, e.g. IL8 levels showed a stronger increase specifically in female SMI patients, while male patients exhibited more pronounced attenuation in Spike antibody levels, but the imbalanced analyses means these results should be interpreted with caution.

Additionally, smoking status was almost entirely confounded by group membership, precluding any meaningful adjustment for smoking behaviour in our analyses. As smoking has been associated with impaired adaptive immune responses to SARS-CoV-2 vaccination in healthy individuals (Ferrara et al., 2022), this discrepancy may explain the observed attenuated antibody response among SMI patients. However, it is not simply a source of noise in this context, but rather a defining feature of the broader clinical profile of individuals with SMI, with recent meta-analytic estimates indicating smoking prevalence of approximately 65 % in schizophrenia, 46 % in bipolar disorder, and 33 % in major depressive disorder (Fornaro et al., 2022). Similarly, other lifestyle-related and medical comorbidities, such as poor nutrition, low physical activity, and metabolic or cardiovascular conditions, are disproportionately prevalent in this population and were not explicitly accounted for in our models.

Importantly, these factors do not diminish the clinical relevance of our findings. On the contrary, they represent real-world contributors to the increased vulnerability of SMI patients. Our study was not designed to isolate a theoretical immune response in idealised conditions, but rather to capture the actual vaccine-induced immune dynamics within a population already known to be medically and socially vulnerable. Even if direct and indirect effects cannot easily be disentangled, reduced vaccine responses still represent real-world risks for these patients, who have a higher chance of severe (Lee et al., 2020) or fatal (Li et al., 2020; Nemani et al., 2021; Vai et al., 2021) outcomes after being infected with COVID (De Picker et al., 2021). Nevertheless, to better understand underlying mechanisms, we emphasise the need for replication in more controlled designs with better-matched groups.

This extends to the type of vaccine administered, which was unevenly distributed across study groups and sites in our study, with all Pfizer vaccinations in the SMI group administered at one location and none at the other. This site-specific distribution, dictated by local vaccination protocols, precluded separate analyses of individual mRNA vaccines (Pfizer vs. Moderna), as such comparisons would be confounded by both study site and diagnostic group. Although vaccine type was statistically controlled for in all models, this remains a limitation that future studies with more balanced and randomised vaccine allocation should address.

Such studies could also further explore the clinical outcomes of attenuated adaptive immune responses, considering that antibody levels may correlate with protection against later infections (Amanatidou et al., 2022), and were ultimately similar across groups. Interpretation of this finding is limited by the elevated baseline antibody levels in SMI patients, which may have introduced ceiling effects that restricted further increases. However, dynamic group differences remained significant after adjusting for baseline antibody levels, suggesting that if both groups had started at similar levels, the SMI group may have ultimately shown significantly lower antibody concentrations. This limitation stems from the opportunistic nature of the study and the imperfect clinical assessment methods available for determining prior exposure. Future studies could address this by using prospective longitudinal

designs that link both absolute and relative immune response to real-world infection outcomes.

In general, our results support the idea of trained innate immunity as a mechanism in SMI pathophysiology and suggest that anti-inflammatory pre-treatment could enhance vaccine efficacy in this population. Future studies using other vaccines, different types of immune challenges, alternative biomarkers, or more tightly controlled intervals between vaccination and measurement are crucial to confirm and extend these findings. Despite the described constraints and remaining questions, the emergence of a discernible signal supports the need for larger-scale immune-challenge studies in SMI populations.

5. Conclusions

This study used SARS-CoV-2 vaccination to model the longitudinal and dynamic responses to an immune challenge in both the innate and adaptive immune systems of SMI patients. We found evidence for an exaggerated innate immune response and attenuated adaptive response in SMI patients, who showed a stronger increase in proinflammatory cytokines IL1 β and IL8 after the first vaccine administration, while levels of antibodies against the SARS-CoV-2 Spike protein and its S1 and S2 subunits increased less in SMI patients than NPCs following one or two vaccine doses. Our work highlights the complex and dynamic nature of immune dysregulation in SMI, and emphasises the importance of using immune challenge designs in immunopsychiatry instead of relying solely on cross-sectional measurements which fail to capture the inherently dynamic nature of immune responses. Finally, both innate and adaptive immune systems deserve to be investigated in parallel as their complex interactions will determine patients' real-world clinical outcomes.

CRedit authorship contribution statement

Tim Rietberg: Formal analysis, Writing – original draft, Writing – review & editing. **Kawtar El Abdellati:** Conceptualization, Writing – review & editing. **Alexandre Lucas:** Methodology, Writing – review & editing. **Margot Lemarinier:** Methodology. **Steven Fried:** Methodology. **Jean-Romain Richard:** Conceptualization, Writing – review & editing. **Ryad Tamouza:** Conceptualization, Resources. **Violette Coppens:** Supervision, Writing – review & editing. **Manuel Morris:** Resources, Writing – review & editing. **Marion Leboyer:** Conceptualization, Resources, Writing – review & editing. **Livia De Picker:** Conceptualization, Methodology, Supervision, Writing – review & editing.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author(s) used the ChatGPT AI language model from OpenAI in order to refine language. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.bbih.2025.101114>.

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