

Research paper

NKG2A and NKp30 expression in NK cells correlates with preserved white matter and cortical thickness and reduced negative symptoms in psychiatric disorders

Alberto Inuggi^{a,1}, Tiziana Altosole^{a,1}, Andrea Escelsior^{b,a,*}, Laura Damele^a, Elisa Cilia^b, Luca Favilla^b, Giacomo Marengo^b, Bruno Sterlini^{c,a}, Chiara Rosa Maria Uras^a, Barbara Parisi^a, Riccardo Guglielmo^b, Beatriz Pereira Da Silva^b, Fabrizio Loiacono^a, Daniela Fenoglio^{d,e}, Gilberto Filaci^{d,e}, Mario Amore^b, Gianluca Serafini^{a,b}, Emanuela Marcenaro^{c,a}

^a IRCCS Azienda Ospedaliera Metropolitana, Genoa, Italy

^b Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health (DiNOGMI), University of Genoa, Genoa, Italy

^c Department of Experimental Medicine, University of Genoa, Genoa, Italy

^d Centre of Excellence for Biomedical Research and Department of Internal Medicine, University of Genoa, 16132, Genoa, Italy

^e Biotherapy Unit, IRCCS Ospedale Policlinico San Martino, Genoa, 16132, Italy



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ABSTRACT

Background and hypothesis: Immune dysregulation contributes to the pathophysiology of schizophrenia (SZ) and bipolar disorder (BD), but specific immune alterations remain unclear. Natural killer (NK) cells, regulated by a balance of activating and inhibitory receptors, are increasingly implicated in neuroimmune interactions. We hypothesized that distinct NK cell receptor expression patterns may identify patient subgroups characterized by preserved brain structure and reduced symptom burden.

Study design: We conducted deep immunophenotyping and unsupervised clustering of NK cells from 53 patients (32 BD, 21 SZ) and 25 healthy controls (HC). Frequencies of NK subsets defined by main receptor expression were examined. A subset of 58 participants also underwent MRI to assess cortical thickness and white matter microstructure. Associations between immune profiles, imaging measures and clinical symptoms were tested.

Study results: Across clustering models, we consistently identified a patient-specific cluster (PSI) characterized by increased NKG2A⁺NKp30⁺ NK cells and reduced double-negative (NKG2A[−]NKp30[−]) NK cells. This pattern was independent of classical CD56-based maturation. Patients in the PSI cluster showed preserved cortical thickness and white matter integrity compared with patients outside the cluster, who exhibited widespread reductions relative to HC controls. Furthermore, reduced double-negative NK frequencies correlated with lower burden of negative symptoms.

Conclusions: Co-expression of NKp30 and NKG2A defines a meaningful NK cell phenotype associated with immune regulation, preserved brain structure, and improved clinical outcomes in SZ and BD. This profile may represent a marker of immune resilience and neuroimmune homeostasis, with potential implications for early diagnosis, patient stratification, and novel therapeutic strategies.

1. Introduction

Schizophrenia (SZ) and bipolar disorder (BD) are severe psychiatric disorders whose etiopathogenesis remains largely obscure. Current

models suggest a multifactorial origin involving genetic, epigenetic, environmental, and immune factors, supported by evidence from epidemiological, genomic, biomarker, and postmortem studies (Gordovez and McMahon, 2020; Halstead et al., 2023; Solmi et al.,

* Corresponding author at: Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, Section of Psychiatry, University of Genoa, Largo Paolo Daneo 3, 16132, Genoa, Italy.

E-mail address: andrea.escelsior@unige.it (A. Escelsior).

¹ Equal contribution.

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2021). The traditional concept of the central nervous system as an immune-privileged site has been challenged by growing evidence of a dynamic interplay between peripheral immune components and brain-resident cells (Galea et al., 2007). Patients with psychosis often show neurovascular dysfunction and increased blood-brain barrier permeability, potentially amplifying immune-brain interactions (Najjar et al., 2017). Lymphocytic infiltration in key brain regions of individuals with psychosis (Schlaaff et al., 2020), along with postmortem evidence of elevated pro-inflammatory gene and protein expression in SZ (Trépanier et al., 2016), further supports the immune-brain interaction hypothesis. While immunopsychiatric research has largely focused on cytokines and T cells, attention is increasingly shifting toward innate immune cells, particularly NK cells and monocytes. As the body's first line of defense, the innate immune system recognizes pathogen-associated molecular patterns through pattern recognition receptors (Riera Romo et al., 2016). NKs, characterized by CD3[−]CD56⁺ surface markers, play multifaceted roles that include direct cytotoxicity as well as the secretion of pro-inflammatory cytokines (Moretta et al., 2001; Vivier et al., 2011). Distinct subsets, such as CD56^{bright} and CD56^{dim} NKs, exhibit specialized profiles in terms of cytokine production and cytotoxic potential (Abel et al., 2018; Marcenaro et al., 2017). Their function is regulated by a finely tuned balance between activating and inhibitory receptors. The main activating receptors include the natural cytotoxicity receptors, namely NKp46, NKp30 and NKp44, which recognize ligands generally expressed/overexpressed on transformed cells, but not on healthy self-tissues. Immune cells are a notable exception, as NK cells interact dynamically with them due to their distinct expression of receptor ligands, which can trigger NK cytotoxicity when dysregulated or autoreactive (Marcenaro et al., 2005). NK cell inhibition is mainly mediated by KIRs (recognizing classical HLA-I alleles), LILRB1 (binding classical and non-classical HLA-I like HLA-G), and CD94/NGK2A (specific for HLA-E). Like T cells, NKs can also express PD-1, modulating their activity further (Marcenaro et al., 2017; Pesce et al., 2017). Despite their key role in immune surveillance, NK cell studies in SZ and BD remain limited and inconsistent, some report reduced NK numbers, particularly in chronic or acute SZ (Karpinski et al., 2018, 2016; Sperner-Unterwieser et al., 1999), while others show increased percentages or no differences at all in NK frequency or cytotoxicity (Cosentino et al., 1996; Fernandez-Egea et al., 2016; McDaniel et al., 1992; Schindler et al., 1986; Yovel et al., 2000). In BD, NK alterations are even less consistent, although some evidence links cytokine-producing NKs to white matter integrity and functional brain connectivity (Furlan et al., 2019). Monocytes, key players in the mononuclear phagocyte system, are involved in host defense and tissue homeostasis and are classified into classical, intermediate, and nonclassical subsets (Passlick et al., 1989). In tissues, they differentiate into macrophages or DCs, exerting pro- or anti-inflammatory effects (Guilliams et al., 2014). The macrophage-T cell theory of schizophrenia (Smith and Maes, 1995) first suggested a role for monocyte activation in psychiatric disorders, now supported by studies reporting elevated monocyte counts in acute SZ and FEP, with partial normalization post-treatment (Steiner et al., 2020; Zhou et al., 2024). Nonclassical monocytes inversely correlate with cortical thickness (Chen et al., 2022). Data on innate immune cells in BD are often inconsistent yet collectively support a model of innate immune dysregulation involving monocytes and NKs in BD and SZ (Barbosa et al., 2015; Becking et al., 2018). NK-cell activity is regulated through the balance between activating and inhibitory receptors, which contribute to immune surveillance and inflammatory regulation (Moretta et al., 2001; Vivier et al., 2011). Among these, NKp30 is involved in NK-cell activation and NK-dendritic cell interactions, whereas NKG2A mediates inhibitory signaling through HLA-E and contributes to immune tolerance (Pesce et al., 2017). Recent evidence suggests that psychotic disorders may be associated not only with quantitative NK-cell alterations, but also with changes in receptor expression, including increased NKG2A and reduced NKp30 expression in first-episode psychosis patients (Tarantino et al., 2021). More broadly, innate immune

dysregulation involving NK cells, monocytes, and macrophages has increasingly emerged as a relevant component of schizophrenia and bipolar disorder pathophysiology (for a review, see Escelsior et al., 2026). Based on these premises, we aimed to investigate NK cells and monocyte subsets through deep immunophenotyping and clustering, and to examine their associations with brain imaging and clinical features in patients with SZ and BD and in health controls (HC).

2. Methods

2.1. Subjects recruitment and clinical assessment

Thirty-two patients diagnosed with BD and twenty-one with SZ, were recruited for our study from the Psychiatry Clinic of the IRCCS Ospedale Policlinico San Martino of Genoa. Sociodemographic and clinical data were collected through a structured psychiatric interview by trained psychiatrists. Inclusion criteria involved patients aged 18 to 65 years with a diagnosis of BD and SZ according to the criteria of the Diagnostic and Statistical Manual for Mental Disorders-Fifth Edition (DSM-5). Exclusion criteria included: 1) past/present substance abuse, 2) clinical history of acute brain damage, neurodegenerative disease, intellectual disability and presence of physically disabling diseases (including acute infectious, inflammatory, autoimmune, oncological, cardiovascular, or metabolic diseases.), 3) contraindications to magnetic resonance imaging (MRI). Additionally, we recruited 25 HC subjects (13 males and 12 females, mean age 32 ± 10.2) with the same exclusion criteria plus the absence of lifetime/current psychiatric disorders and HAM-D score lower than 8 and a YMRS score lower than 7. For SZ and BD patients, the dosages of antidepressants, mood stabilizers, antipsychotics and benzodiazepines were converted into chlorpromazine, lithium, imipramine and diazepam equivalents respectively (Baldessarini, 2013). The recruitment interview included several assessment tools such as the Mini International Neuropsychiatric Interview (MINI), the Positive and Negative Syndrome Scale (PANSS), the Young Mania Rating Scale (YMRS), and the Hamilton Depression Rating Scale (HAM-D). Fifty-eight participants also underwent an MRI session to evaluate their brain structural integrity. The study was approved by the Regional Ethics Committee (CER Liguria: 366/2019), informed consent was obtained from each patient prior to their participation in the study.

2.2. Peripheral blood data

2.2.1. Collection

Blood samples were collected on the same day as the MRI session, 1–2 h before image acquisition. MRI acquisitions were performed within fixed afternoon time slots (14:00–17:00); accordingly, blood sampling was consistently performed between 12:00 and 15:00 in order to reduce potential circadian variability.

2.2.2. Preparation of peripheral blood mononuclear cells (PBMC)

Peripheral blood (PB) has been collected from all subjects in tubes containing sodium heparin. PBMCs have been isolated from whole peripheral blood using Ficoll-Hypaque (CEDARLANE's Lympholyte® Cell Separation density gradient centrifugation media). PBMCs have been then washed and resuspended in Dulbecco's Phosphate Buffered Saline to perform immunophenotype.

2.2.3. Antibody staining and sample acquisition

Staining was performed on 1×10^6 PBMC recovered from PB of each patient. Priorly, the cells were incubated with Fixable Viability stain (FVS 620, c.n. 564996, Becton Dickinson) and then with the antibodies cocktail as described in Table S1 for NKs and Table S2 for monocytes cells detection. After the incubation, samples were washed with PBS $1 \times$ and resuspended for the acquisition with LSR Fortessa X20 flow cytometer (BD). All the mAbs used were mouse-anti human. The same lots of fluorochrome-conjugated mAbs have been used throughout the study.

The instrument was daily calibrated. All the files have been saved in FCS 3.0 format and exported to be analyzed with FlowJo 10.10 software with supervised gating analysis.

2.2.4. Gating strategy to detect NK cells

To identify NK cell population, the following gating strategy were performed: FVS-620 vs FSC-Area plot to exclude dead cells; FSC-Area vs FSC-Height plot to eliminate doublets; SSC-Area vs FSC-Area to select low side scatter cells; CD56 vs CD3 plot to discriminate between NK CD56⁺ cells and CD3⁺CD56^{+/-} cells; CD56 vs CD16 plot to define NK cell subsets: CD56^{br} CD16⁻, CD56^{br} CD16^{dim}, CD56^{dim} CD16⁺ and CD56^{br} CD16^{br}. Within CD56^{dim} CD16⁺ cell subset, NKG2A⁻NKG2C⁺ CD57⁺ cells were gated as adaptive NKs (Della Chiesa et al., 2016; Pesce et al., 2019). For each NK subset, the expression of several activating and inhibitory receptors in terms of positive cell frequency was assessed.

2.2.5. Gating strategy to detect monocytes

To identify monocyte populations the following gating strategy has been performed: FVS-620 vs FSC-Area plot to exclude dead cells; FSC-Area vs FSC-Height plot to eliminate doublets; SSC-Area vs FSC-Area to select high side scatter cells; HLA-DR vs CD11c plot to discriminate between monocytes (HLA-DR⁺ CD11c⁺) and myeloid dendritic cells (HLA-DR⁺ CD11c⁻). Finally, the monocytes subpopulations were identified with CD14 vs CD16 plot: classical (CD14⁺⁺CD16⁻) and intermediate (CD14⁺⁺CD16⁺) and nonclassical (CD14^{+/-} CD16⁺⁺). The expression of CCR2 and CD36 markers in terms of positive cell frequency in all monocytes subsets has been assessed.

ELISA analysis for the detection of HCMV seropositivity was described in Supplementary Materials.

2.3. Statistical analysis

2.3.1. Demographic

Non-parametric tests (Kruskal-Wallis and pairwise, False Discovery Rate (FDR) corrected, Wilcoxon tests for post hoc analysis) and Fisher Chi-square were run to compare continuous and categorical variables between subjects divided by *diagnosis* (BD, SZ, HC).

2.3.2. Immunophenotyping

2.3.2.1. NK cells

2.3.2.1.1. NK cells stratification. We first (model #1) stratified NKs according to their main population (factor *POP*, levels: CD56^{br} CD16⁻, CD56^{br} CD16^{dim}, CD56^{dim} CD16⁺ and CD56^{br} CD16^{br}). Then we created a second factor (*REC*) calculating, for each of the above population, the frequency of the four main receptors (NKP46, NKP30, NKG2A, HLA-DR) and of the population (OVERALL) itself with respect to the total NKs. In a second model (#2), whom utility will be later clarified, *REC* factor was defined as the frequency of the activation, or not, of NKP30 and NKG2A receptors, obtaining four different levels: NKG2A⁺NKP30⁺, NKG2A⁻NKP30⁺, NKG2A⁺NKP30⁻, and NKG2A⁻NKP30⁻. Additional models were tested and described in Supplementary Materials.

2.3.2.1.2. Subjects' stratification. Subjects were stratified according to (A) clinical *diagnosis* (levels: BD, SZ and HC) and (B) by data-driven clustering. The latter approach consisted in running a principal component analysis (PCA, FactoMineR R package) over the twenty values defined in gating #1 and feeding a K-means clustering algorithm with its first five components. Three different cluster numbers were tested: $k = 3$ (one for each population) and then we increased and decreased it by one ($k = 2$ and $k = 4$) and we selected that k that maximized the mean silhouette coefficient (Rousseeuw, 1987), the ratio between within-cluster cohesion and nearest-cluster separation.

2.3.2.1.3. Factorial analyses and post hoc. We thus run two factorial analysis using cells stratification #1 with subjects' stratification A and B (models A1, B1) and then, to better interpret their results, we run other

two factorial analyses using cells stratification #2 (models A2, B2). Since data were not normally distributed (verified with Shapiro-Wilk test), factorial analysis was run with the non-parametric, permutation based, AOVPERM R' function and in all models, data was corrected for subjects' age and sex. Post-hoc analyses of the significant interaction between *diagnosis/diagnosis_cluster* and either *POP* or *REC* were performed according to the following schema: in each level of *POP/REC* we run a non-parametric Kruskal-Wallis or Mann-Whitney tests (respectively for three or two factor levels) on *diagnosis/diagnosis_cluster* factor after having removed the effect of age and sex from the data. To be considered significant, p -values had to result <0.05 after having been corrected for multiple comparison through the false discovery rate (FDR) criteria. The further post-hoc of Kruskal-Wallis tests on three levels factors were run with non-parametric Wilcoxon rank sum tests pairwise comparisons, again FDR corrected. Kruskal-Wallis statistical measure will be denoted as H, Mann-Whitey's one as W.

2.3.2.2. Monocyte cells. Monocyte cells were stratified using classical (CD14⁺⁺CD16⁻), intermediate (CD14⁺⁺CD16⁺) and non-classical (CD14^{+/-}CD16⁺⁺) cells as levels of the *POP* factor and the geometric mean of the following receptors: HLA-DR, CD36, CCR2, as *REC* one. PCA + k-means clustering analysis failed to individuate a cluster of only patients; accordingly, the above model was investigated considering only *diagnosis* (BD, SZ, HC) factor. Factorial and post-hoc analyses were run with the same principles and methods as NK ones.

2.3.3. Clinical diagnosis differences and relations with cellular populations

Clinical differences between patients were examined using a two-ways ANCOVA including factors *diagnosis* and *cluster* and age, sex, and disease duration entered as covariates. Analyses were conducted using the AOVPERM function in R. In addition, non-parametric correlation analyses were run between clinical scores and cellular populations of interest.

2.4. MRI data

2.4.1. MRI data acquisition

Images were acquired on a 3 T Siemens Prisma scanner using a 64-channel Head/Neck coil. To reduce head motion and improve subject comfort, foam pads were employed. Three-dimensional T1-weighted structural images were acquired using a 3D MPRAGE sequence with the following parameters: TE: 2.96 ms, TR: 2300 ms, TI: 919 ms, Flip Angle: 8°. Two-hundred-fifty-six slices with voxel Size: $1 \times 1 \times 1 \text{ mm}^3$ were acquired in sagittal orientation. Diffusion-weighted images were acquired using a spin-echo echo-planar imaging (EPI) sequence with the following parameters: TR: 3200 ms, TE: 63 ms, Flip Angle: 90°, Echo Spacing: 0.27 ms. FOV: 220 mm. Eighty-one slices with Voxel Size: $2 \times 2 \times 2 \text{ mm}^3$ were acquired with axial orientation. The diffusion sensitizing gradients were applied along 64 non-collinear directions ($b = 1000 \text{ s/mm}^2$), together with 8 acquisitions without diffusion weighting ($b = 0$).

2.4.2. MRI data processing

2.4.2.1. Cortical thickness (CT) analyses. Cortical thickness was calculated from 3D T1-weighted MRI scans using the default pipeline of the Computational Analysis Toolbox (CAT, version 12.8), within SPM12 using MATLAB (version 2023b). Finally, subjects' CT surface images were smoothed (FWHM = 15 mm) and resampled, to a 32 k mesh compatible with the Human Connectome Project (HCP). Methodological details are described in supplementary materials.

2.4.2.2. Diffusion data analysis

2.4.2.2.1. Individual pre-processing. The diffusion-weighted data were skull-stripped using the Brain Extraction Tool implemented in FSLv6.0 (<http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/>) and then corrected for

distortions caused by eddy currents and movements. The diffusion tensor (DT) was estimated on a voxel-by-voxel basis using the DTifit toolbox, part of the FMRIB Diffusion Toolbox within FSL, to obtain fractional anisotropy (FA), mean (MD), axial (AD), and radial (RD) diffusivities maps, the latter obtained by averaging L2 and L3 images. A GPU-based bedpostX processing (Hernández et al., 2013) was done on eddy-current corrected images to allow probabilistic tractography analysis later.

2.4.2.2. TBSS analysis. A tract-based spatial statistics (TBSS) was performed on the whole group. Individual FA images of all subjects were non-linearly registered to a standard fractional anisotropy template (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FMRIB58_FA). We did not create a study-specific skeleton template, but we non-linearly reported each subject's fractional anisotropy map to the FMRIB58 skeleton (parameter -T in the tbss_3_postreg script). This was performed to better segment our results with the xTRACT atlas (Warrington et al., 2020). The same operations were subsequently applied to the individual mean, axial, and radial diffusivity images using the previously calculated transformation. Voxelwise cross-subject statistics were then applied to these data. Then we calculated the overlap percentage of each significant TBSS map with each tract defined in xTRACT atlas (Escelsior et al., 2024, 2023) to better describe which main tracts were affected by a specific statistical

contrast. Methodological details are described in supplementary materials.

2.4.3. Statistical analysis

Concerning whole brain imaging data, regardless of the specific implementation of either FSL (for TBSS) or SPM (for CT) software, the same General Linear Models were tested. We first assessed age and sex corrected group differences, either dividing subjects according to their *diagnosis* (HC, BD, SZ) or *diagnosis_cluster* (PSIPSI, PSIMIX, HCMIX). Second, only of those cells' populations that resulted of significant interest in our previous analyses, we investigated their correlation with patients' structural integrity correcting for subjects' age, sex and disease duration. Multiple comparisons correction was done in each specific MRI analysis package using family-wise error (FWE) for CT analyses in SPM and threshold-free cluster enhancement (TFCE) correction for TBSS analyses in FSL. Significance threshold was set to $p < 0.05$.

2.5. Analyses responsibilities

All the data and analyses were collected within the Ospedale Policlinico San Martino of Genoa. Clinical scales' values were compiled by trained psychiatrists of the Psychiatry Clinic. Frequencies of NKs and

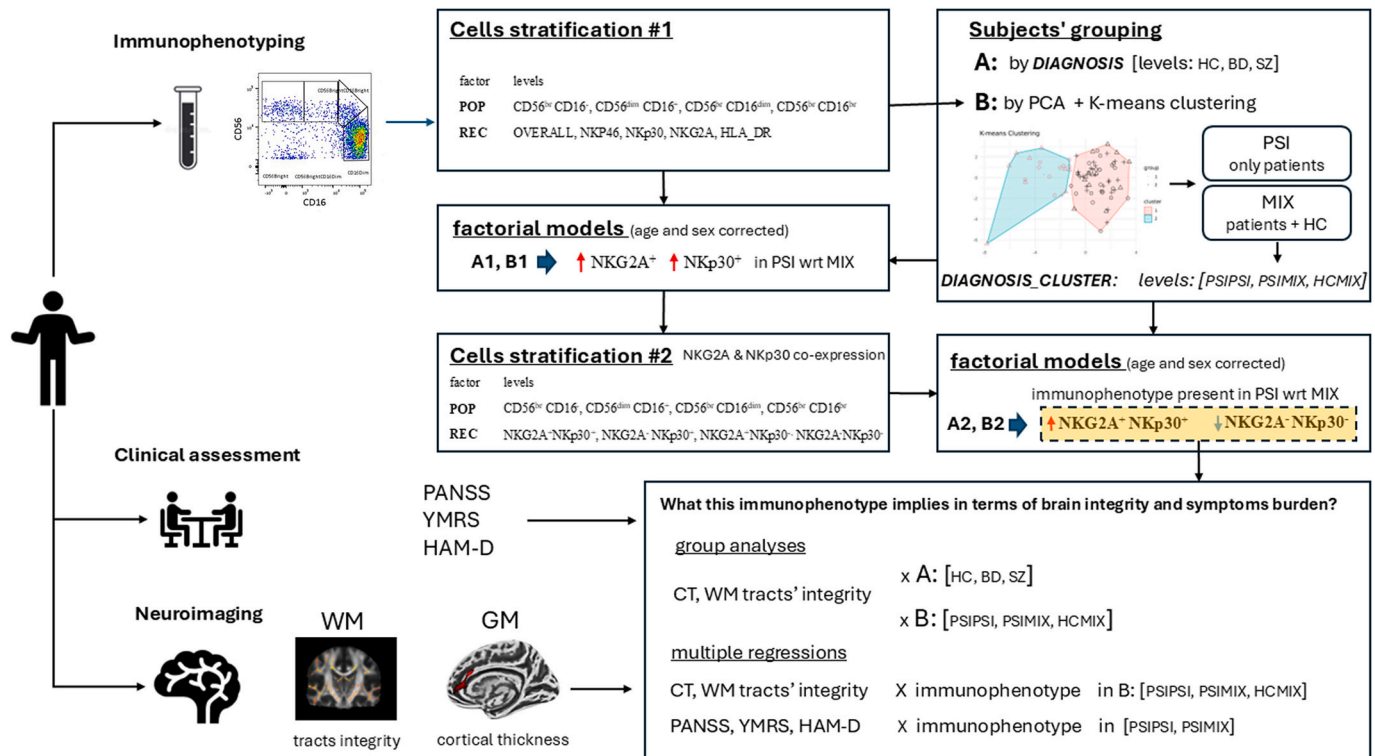


Fig. 1. Summary of NKs analyses. Subjects' peripheral blood mononuclear cells (PBMC) underwent a first (#1) gating strategy that calculated the (OVERALL) frequency of each main NKs population (CD56^{br} CD16⁻, CD56^{dim} CD16⁺, CD56^{br} CD16^{dim}, CD56^{br} CD16^{br}) and, within each of them, the frequency of cells expressing one of these receptors (NKP46, NKP30, NKG2A, HLA_DR). Differences in this 5 × 4 model were compared across: A) factor *diagnosis* (healthy controls, HC, and patients with bipolar disorder, BD, and schizophrenia, SZ), and B) data-driven subjects clustering. B levels were determined by running a principal component analysis (PCA) of these 5 × 4 columns dataset and feeding a K-means clustering algorithm with its first five components. The algorithm individuated two different clusters (PSI and MIX): one composed of only patients, and one composed of patients and controls. Levels of factor B (*diagnosis_cluster*) were thus: PSIPSI, PSIMIX and HCMIX. We then ran two (A1 and B1) mixed factorial models combining cell stratification #1 with both subjects' grouping A and B, which showed that PSIPSI patients had higher frequencies of NKG2A⁺ and NKP30⁺ cells. To evaluate whether these increments were driven by a same population of cells that over-expressed both these receptors (NKG2A⁺NKP30⁺, double positivity) or by two populations that each over-expressed just one of them (NKG2A⁻NKP30⁺, NKG2A⁺NKP30⁻), we run a second cell gating/stratification (#2) classifying, for each main NK family, the percentage of cell according to the expression, or not, of those two receptors. Analysis B2 defined that in the patients belonging to the PSI cluster, compared to the other subjects, there was an increment of NKs with double positivity at the expense of those not expressing any of them (double negativity). Clinical and MRI data were used to relate this specific immunophenotype pattern to both brain integrity and clinical symptoms burden. By structured interview we calculated PANSS, YMRS, HAM clinical scales. By T1-weighted MRI sequence, we got subjects gray matter (GM) integrity, in terms of cortical thickness, and by diffusion-weighted sequence, xTract and TBSS software, we got the structural integrity of the main white matter (WM) tracts. Clinical and MRI data and frequency of cells with double positivity and negativity were compared across patients by diagnosis and cluster and correlated together in age, sex and disease duration corrected multiple regression models.

monocytes cells were extracted from personnel of the CYMACS facility. Individual anatomical assessments were run with automated scripts by expert bioengineer of Life Science Computational lab (LISCOMP). All these steps were run by people blinded to the other outcomes. Final statistical analysis and neuroimaging group analysis were run on an anonymized dataset.

3. Results

A schema of the analyses performed were summarized in Fig. 1 and detailed in the following paragraphs. Additional analyses, including also those stating the absence of any significant effects of HCMN seropositivity on present results, were included in supplementary materials.

3.1. Demographic and clinical characteristics

All patients were recruited from an inpatient psychiatric unit during hospitalization for an acute mood episode requiring clinical admission. At the time of enrollment and MRI acquisition, patients were in partial symptomatic remission, with sufficient clinical stability to undergo MRI scanning and study assessments. Among bipolar disorder patients, 12 patients were experiencing a manic episode, 12 a depressive episode, and 8 a mixed episode. Participants' demographic data are summarized in Table 1A. An effect of age was found across groups (Kruskal-Wallis chi-squared = 7.95, $p = 0.016$), although post hoc analysis only found trends differences among groups (BD vs SZ = 0.072, BD vs HC = 0.051, SZ vs HC = 0.072). Sex was not different (X-squared = 2.58, p -value = 0.27) across groups.

3.2. Immunology

3.2.1. NK cells

3.2.1.1. Subjects clustering. Preliminary PCA analysis revealed that a specific set of cell populations, primarily expressing the NKG2A and NKp30 receptors, strongly contributed to the first principal component. Results of three clustering levels ($k = 2, 3, 4$) are summarized in Fig. S1. Silhouette ratios were $k = 2$: 0.319, $k = 3$: 0.229, $k = 4$: 0.212, suggesting that the two-cluster solution provided the best trade-off between cluster separation and cohesion. Such clustering defined one cluster

(PSI) composed of only patients (but one control) and one (MIX) composed by a mix of patients and controls (Fig. 2B, Table 1B). Subjects' stratification B thus defined a new *diagnosis_cluster* factor with three levels: PSIPSI (patients in cluster PSI), PSIMIX (patients in cluster MIX) and HCMIX (healthy controls in cluster MIX). The single control in cluster PSI was thus excluded from these analyses. Subjects' factors were summarized in Table 2.

3.2.1.2. Factorial analyses. Details of analyses statistical power were summarized in Table 3.

Model A1

Factorial analysis of the effects of diagnosis on NKs main population and receptors frequencies found an interaction only between *receptor* and *diagnosis*. Post hoc analysis found an effect of *diagnosis* in NKp30 and NKG2A, with higher (+ 58.5%) values in SZ compared to controls in the former and in SZ compared to both controls (+ 85.6%) and BD (+ 74.8.6%) in the latter.

Model B1

We run factorial analysis substituting *diagnosis* with *diagnosis_cluster* factor (model B1) and found it interacting only with REC. Posthoc analysis found that the frequencies of NKp30 and NKG2A receptors were higher in PSIPSI with respect to both PSIMIX (NKp30: +69%, NKG2A: +1868%) and HCMIX (NKp30: +93%, NKG2A: +654%). Results are displayed in Fig. 3C. Increased frequencies of NKG2A⁺ and NKp30⁺ in PSIPSI compared to PSIMIX could be confirmed for both BD and SZ (Fig. S5).

Model B2

Once observed that NKG2A⁺ and NKp30⁺ expressions were able to identify a subpopulation of patients that differed from all other individuals, we tried to evaluate whether these increments were driven by either a same population of cells that over-expressed both these receptors or by two populations that each over-expressed just one of them. Results of un-clustered subjects (analysis A2) were of minimal interest and were thus reported only in Supplementary Materials (Fig. S2). Those following the cluster analysis (model B2), revealed a significant *diagnosis_cluster* × REC interaction and its post hoc analysis revealed a concomitant increase in NKs co-expressing both receptors (+ 2926%) and a decrease (−68%) in cells lacking both receptors, in patients belonging to the PSI cluster compared to subjects in the MIX cluster (Fig. 2D). Average values were summarized in Table 3.

Table 1

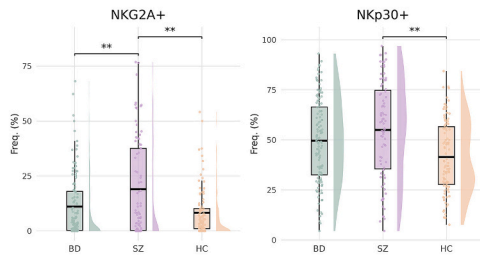
A) Demographic characteristics of patients with bipolar disorder (BD), schizophrenia (SZ) and healthy controls (HC), with and without MRI session. B) composition by diagnosis of the two clusters. C) subjects that underwent MRI recordings divided by diagnosis and cluster.

A) Demographics						
	Without MRI (78)			With MRI (58)		
	BD	SZ	HC	BD	SZ	HC
Sample size	32	21	25	20	15	23
# Male/Female	22/10	13/8	13/12	14/6	11/4	12/11
Age mean ± SD	44.3 ± 14	38.7 ± 12.2	32 ± 10.2	44 ± 15	35.8 ± 9.4	32.2 ± 10.5

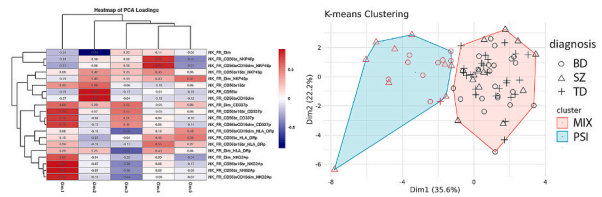
B) Clusters composition				
#	Without MRI (78)		With MRI (58)	
	TOT	HC	SZ	BD
MIX	59	24	12	23
PSI	19	1	9	9

C) Cohort with MRI				
Diagnosis		Cluster (HC, BD, SZ)		
HC	BD	SZ	PSI	MIX
23	20	15	8 (1/3/4)	50 (22/17/11)

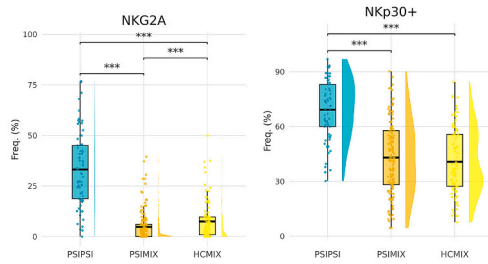
A: model A1 – NK main POP x REC x diagnosis



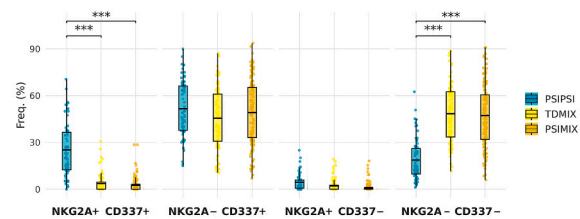
B: PCA + k-means clustering



C: model B1 – NK main POP x REC x diagnosis_cluster



D: model B2 – NKG2A, Nkp30 coactivation x diagnosis_cluster



E: MONOCYTE

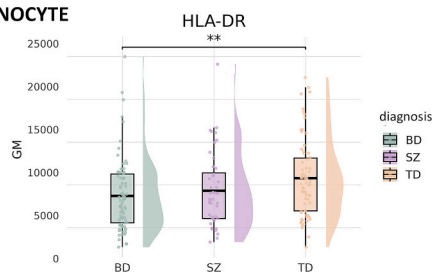


Fig. 2. A) Results of the diagnosis effect in model A1. Frequency of cells expressing NKP30 and NKG2A. B) results of PCA and k-means clustering using the values of the columns of cells stratification #1. C) Results of B1: patients belonging to PSI cluster showed, with respect to individuals in the MIX cluster, higher frequencies of cells expressing the NKG2A and NKP30 receptors. D) Results of B2 model. While cells expressing only one of the two receptors did not vary across clusters, patients belonging to the PSI cluster showed higher frequencies of cells expressing both NKG2A and NKP30 receptors at the expense of those not expressing any of them. E) Effect of diagnosis on the frequency of monocytes cell expressing the HLA-DR receptor. BD showed significant reduction with respect to TD.

Table 2

NK cells and groups stratifications. (cells) POP levels are the four main NKs populations, REC levels are (#1) the frequencies of the cells expressing the listed receptor or (OVERALL) the frequency of that population with respect to the whole NKs cells or (#2) the percentage of cells, for each POP, expressing both NKG2A and Nkp30 receptors, only one of the two or none of them. (groups) HC: healthy controls, SZ: schizophrenic patients, BD: bipolar disorder patients, PSIPSI: patients belonging to the PSI cluster, PSIMIX: patients belonging to the MIX cluster, HCMIX: healthy controls belonging to the MIX cluster.

Cells stratification		
	Factor	Levels
#1 FREQ of main populations and receptors	POP	CD56 ^{br} CD16 ⁻ , CD56 ^{dim} CD16 ⁺ , CD56 ^{br} CD16 ^{dim} , CD56 ^{br} CD16 ^{br}
	REC	OVERALL, NKP46, NKP30, NKG2A, HLA-DR
#2 FREQ of co-expression of NKG2A and Nkp30 receptors	POP	CD56 ^{br} CD16 ⁻ , CD56 ^{dim} CD16 ⁺ , CD56 ^{br} CD16 ^{dim} , CD56 ^{br} CD16 ^{br}
	REC	NKG2A ⁺ Nkp30 ⁺ , NKG2A ⁻ Nkp30 ⁺ , NKG2A ⁺ Nkp30 ⁻ , NKG2A ⁻ Nkp30 ⁻
Groups stratification		
	Name	Levels
A	Diagnosis	BD, SZ, HC
B	Diagnosis_cluster	PSIPSI, PSIMIX, HCMIX

3.2.1.3. Clinical differences between patients belonging to the two clusters.

Clinical scores, divided by diagnosis and clusters they belong to, were summarized in Table 4A. Significant main effects and interactions on these clinical scores within the patient groups and clusters were summarized in Table 4B. The only clinical correlation identified was with medication dosage. Specifically, post hoc analyses revealed that SZ patients in the PSI cluster were prescribed a respectively higher mood stabilizers ($W = 3.94, p < 0.001$) and lower antipsychotic ($W = 2.64, p = 0.008$) dosages compared to those in the MIX cluster. To assess whether this difference could have influenced the previous findings, we replicated B1 and B2 analyses adding both the mood stabilizers and antipsychotic dosages as further covariates. Results were all confirmed and thus opted to report those without this correction. To establish a relationship between clinical scores and NKs characteristic, we run spearman correlation analysis between NKG2A⁺Nkp30⁺, NKG2A⁻Nkp30⁻ and each clinical score, separately for SZ and BD. Particularly in BD, we found various trend of positive correlation between psychotic symptoms and the frequency of cells not expressing any of the two receptors and negative with cells expressing both. These trends reached significance for PANSS N in both groups and PANSS T in BD (Table 4). Taken together, these correlations suggest that the pattern shown by patients belonging to PSI cluster (increased co-expression of both NKG2A and Nkp30 at the expense of cells not expressing any of them) is associated with reduced psychotic symptoms. (See Table 5.)

3.2.2. Monocyte cells

A *diagnosis* × REC interaction ($F = 6.77, p = 0.0002$) was found on

Table 3

Results of the three factorial model designed. Neither the main effect of diagnosis / diagnosis_cluster nor its interaction with POP resulted significant in any of these models. A1: main populations and receptors $\times$ diagnosis, B1: main populations and receptors $\times$ diagnosis_cluster, B1: main populations and receptors $\times$ diagnosis_cluster.

A1: main populations and receptors $\times$ diagnosis			
Diagnosis $\times$ REC: F = 5.48, p = 0.0002			
Post-hoc of diagnosis effect			
In NKp30	H = 12.58, p = 0.0092	SZ > HC	W = 3.63, p = 0.00083
In NKG2A	H = 6.53, p = 0.047	SZ > HC	W = 3.38, p = 0.0012
		SZ > BD	W = 3.33, p = 0.0012
B1: main populations and receptors $\times$ diagnosis_cluster			
Diagnosis_cluster $\times$ REC: F = 48.83, p = 0.0002			
Post-hoc of diagnosis_cluster effect			
In NKp30	H = 76.87, p < 0.0001	PSIPSI > PSIMIX PSIPSI > HCMIX	W = 8.11, p < 0.0001 W = 8.10, p < 0.0001
In NKG2A	H = 124.69, p < 0.0001	PSIPSI > PSIMIX PSIPSI > HCMIX	W = 10.67, p < 0.0001 W = 8.16, p < 0.0001
B2: coactivation of NKG2A and NKp30 $\times$ diagnosis_cluster			
Diagnosis_cluster $\times$ REC: F = 6.79, p = 0.0002			
Post-hoc of diagnosis_cluster effect			
In NKG2A ⁺ NKp30 ⁺		PSIPSI > PSIMIX PSIPSI > HCMIX	W = 11.14, p < 0.0001 W = 9.19, p < 0.0001
In NKG2A ⁻ NKp30 ⁻		PSIPSI < PSIMIX PSIPSI < HCMIX	W = 8.72, p < 0.0001 W = 8.64, p < 0.0001

monocytes cells. Post hoc analysis revealed a significant effect of diagnosis factor (H = 10.57, p = 0.015) only on cells expressing the HLA-DR receptor. Both patients' groups had reduced geometric mean that HC, but only BD were significant (BD: W = 2.95, p = 0.009, SZ: W = 1.7, p = 0.11) as shown in Fig. 2E.

3.3. MRI analysis

To understand whether the coactivation of NKG2A and NKp30 receptors was associated with an altered brain structural integrity, we analyzed the MRI data of the fifty-eight subjects (see Table 1C) that underwent an MRI session.

3.3.1. White matter integrity

We first ran a preliminary analysis on diagnosis (BD, SZ, HC) differences in white matter structural integrity. We found that only BD patients, and not SZ, showed signs of reduced structural integrity (lower FA and higher RD) in various tracts. Corresponding maps were displayed in Fig. S9 and tracts involved in this altered pattern were summarized in Table S5. Then we compared structural integrity across subjects divided according to diagnosis_cluster factor. PSIMIX showed a widespread reduced structural integrity (lower FA and higher RD) compared to HCMIX (Fig. 3A, Table S6). PSIPSI was not significantly different from HCMIX and showed (Fig. S10) an increased structural integrity compared to PSIMIX only in 7.27% of the forceps minor (fmi). Considering all the patients' cohort, correlations between their structural integrity and frequency of cells co-expressing NKG2A and NK30 and those exhibiting double negativity were displayed in Fig. 3B and summarized in Table 6.

3.3.2. Cortical thickness

We first ran a preliminary analysis on diagnosis (BD, SZ, HC) differences in cortical thickness, finding a much wider pattern of reduced CT in SZ (Fig. S11, left) compared to BD (Fig. S11, right) with respect to HC, with regions positions summarized in Table S7. We then compared structural integrity across subjects divided according to diagnosis_cluster factor. PSIMIX showed a widespread reduction of CT compared to HCMIX and a more focal reduction compared to PSIPSI (Fig. 4A, Table 6). Correlating the CT of all the patients' cohort with both frequency of cell co-expressing NKG2A and NKp30 and with those exhibiting double negativity we found a widespread pattern of positive correlation with former and negative with the latter. As occurred for white matter integrity, higher structural integrity was associated with increments of NKG2A⁺NKp30⁺ and reduction of NKG2A⁻NKp30⁻ (Fig. 4B, Table 6).

4. Discussion

The main result of this study is that patients may be distinguished from controls not by classical NK cell subset distribution (e.g., CD56^{bright/dim}) or maturation status alone, but rather by the specific pattern of surface receptor expression. Specifically, our deep phenotyping approach, based on NK cell surface molecule expression and unsupervised clustering, identified a cluster of only patients (PSIPSI) characterized by a distinct immunophenotypic profile consisting in higher frequency of double-positive (NKG2A + NKp30⁺) NKs and a concurrent reduction of double-negative (NKG2A⁻NKp30⁻) NKs, that was related to reduced negative symptoms burden and preserved brain structure.

4.1. Structural alterations and symptoms burden related to NK phenotype

White matter analysis showed a reduced white matter integrity (lower FA and higher RD) in most of the main tracts (Fig. 3A, Table S4) of patients in MIX compared to HC. Conversely, PSIPSI subjects were largely indistinguishable from HCMIX in terms of white matter structure, but also showed a localized increase, with respect to PSIMIX, in FA within a small portion (7.27%) of the forceps minor (Fig. S10). Correlations between diffusion metrics and NK cell subsets showed that lower frequencies of double-negative NKs were broadly associated with greater white matter integrity, while the pattern associated with double-positivity cells was present but more limited in extent (Fig. 3B, Table 6). Notably, in both profiles, the forceps minor emerged as a key tract, along with others primarily involving frontal regions - e.g. the anterior thalamic radiation and frontal aslant - or anterior portions of long-range association tracts. Cortical thickness analysis further supported the role of frontal regions, showing greater preservation in left inferior frontal gyrus and frontal pole in PSIPSI compared to PSIMIX, and negative correlations with NKG2A⁻NKp30⁻ cell frequencies in the anterior insula, anterior cingulate cortex (ACC), and paracingulate cortex. Furthermore, patients lacking the double-positivity pattern exhibited reduced CT relative to HC individuals, predominantly in frontal regions (Fig. 4A). This pattern of mainly frontal structural preservation was paralleled by a general trend toward reduced symptom burden, associated with higher NKG2A⁺NKp30⁺ and lower NKG2A⁻NKp30⁻ frequencies, reaching statistical significance for PANSS Negative scores in both patient groups with low double-negative NKs. While no direct correlation between structural alterations and symptom severity was identified, the convergence of immune and imaging findings strongly supports their relevance and internal consistency. The PANSS scale has been originally designed to put in relation schizophrenics patients positive and negative symptoms with their global psychopathology (Kay et al., 1987), but it is commonly used also in bipolar disorder, despite the interpretation of certain items may differ across the two diagnoses (Anderson et al., 2017; Canuso et al., 2008; Lindenmayer et al., 2008). The PANSS-N specifically evaluates two domains: social amotivation

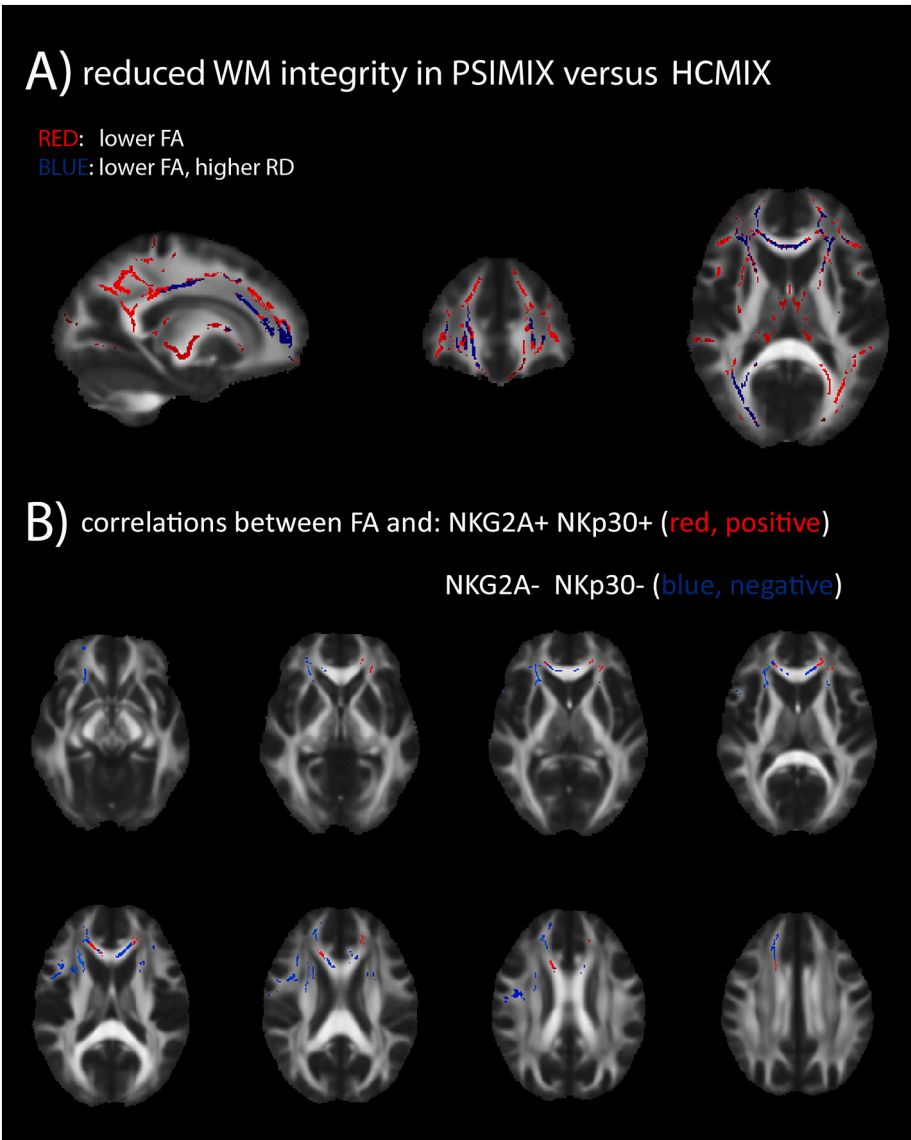


Fig. 3. A) Structural integrity reduction in PSIMIX compared to HCMIX. In red, reduction of FA, in blue reduction of FA and increment of RD. B) Regions of positive (vs NKG2A⁺NKp30⁺) and negative (vs NKG2A⁻NKp30⁻) correlations with FA in patients. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 4

Frequency of the population expressing or not expressing NKG2A and NKp30 receptors divided by diagnosis and cluster, expressed as median and interquartile range. HCMIX: healthy controls belonging to the MIX cluster. BDMIX: bipolar disorder patients belonging to the MIX cluster, SZMIX: schizophrenic patients belonging to the MIX cluster, BDPSI: bipolar disorder patients belonging to the PSI cluster, SZPSI: schizophrenic patients belonging to the PSI cluster.

Diagnosis in cluster	NKG2A ⁺ NKp30 ⁺	NKG2A ⁻ NKp30 ⁻	NKG2A ⁺ NKp30 ⁻	NKG2A ⁻ NKp30 ⁺
HCMIX	2.1 (0.8–5.5)	48.6 (36.1–59.5)	0.9 (0.2–2.1)	47.9 (33.3–59)
BDMIX	2.1 (0.6–3)	44.8 (41.2–57.2)	0.3 (0–0.9)	49.2 (40.5–56.9)
SZMIX	0.9 (0.1–3.4)	41.5 (31.8–69.7)	0.3 (0.1–0.5)	54.1 (30.1–67.1)
BDPSI	20.4 (14.7–22.8)	22.4 (16.2–24.3)	2.6 (1.8–3.4)	55.2 (46.3–66)
SZPSI	32.6 (14.7–38.8)	15.8 (13.1–19.4)	4.2 (1.8–8.2)	46 (40.4–51.8)

and diminished expression. The former is thought to be mediated by a reward-seeking circuit centered on ventral striatum (Kaliuzhna et al., 2020) and connected caudally with the dentate nucleus of the cerebellum and rostrally with orbitofrontal cortex (OFC) and dorsolateral prefrontal cortex (DLPFC) through Supero-Lateral Branch of the MFB (Coenen et al., 2012). Notably, the rostral part of slMFB overlaps with ATR and the two tracts may be confused when not specifically reconstructed, as occurred with automatic tools like xTRACT. ATR is one of

the tracts whose structural integrity here correlated with the NK cell phenotype and the cortical thinning here shown by patients without such phenotype largely embraced DLPFC. Moreover, most of the regions and tracts here found associated with the protective NK phenotype pattern have been systematically associated to negative symptoms burden. In cohorts of schizophrenic patients characterized by negative symptoms, gray matter volume reduction in insula, ACC, parahippocampal gyrus and medial frontal gyri (Koutsouleris et al., 2008;

Table 5

A) Mean clinical scores divided by diagnosis and cluster. SZPSI: schizophrenic patients belonging to the PSI cluster, BDPSI: bipolar disorder patients belonging to the PSI cluster, BDMIX: bipolar disorder patients belonging to the MIX cluster, SZMIX: schizophrenic patients belonging to the MIX cluster. B) Significant main effect of diagnosis and cluster, and their interaction, over clinical scores. C) Correlations between clinical scores and population showing double-positivity (NKG2A⁺NKp30⁺) or double-negativity (NKG2A⁻NKp30⁻) to NKG2A and NKp30 expressions. Significant correlations are marked in bold. SZ: schizophrenic patients, BD: bipolar disorder patients.

A) Clinical scores				
Clinical score	BDMIX (21)	BDPSI (10)	SZMIX (13)	SZPSI (9)
Disease duration	10 (6.5–21.5)	20 (5–23)	15 (5.5–23.2)	7 (5–14)
Therapy (dose equivalents)				
Antipsychotics	220 (150–320)	300 (97–500)	370 (196.2–631.5)	167 (125–187)
Mood stabilizers	1077.5 (720–1305)	1050 (900–1140)	0 (0–72)	780 (360–1000)
Benzodiazepines	9.8 (0–12.4)	0 (0–10)	6.2 (2.2–10.6)	1.9 (1.2–2.6)
Antidepressants	0 (0–55.8)	0 (0–58)	0 (0–0)	0 (0–0)
Clinical scales				
HAM-D	10 (7.2–18.5)	9 (6–16)	12 (9.5–16.5)	12 (7–13)
HAM-A	8.5 (4.2–13)	9 (5–11)	7 (3.5–8.5)	6 (5–10)
PANSS-P	9 (7–18.5)	9.5 (7–14.5)	16.5 (14.5–21.5)	17 (13–19)
PANSS-N	9 (7–14)	7 (7–8.8)	16 (10–27)	14 (7–22)
PANSS-G	31 (26.2–38.8)	24 (19.2–33.2)	38.5 (31.2–48.2)	40 (29–43)
PANSS-TOT	53 (47–68.5)	42.5 (34.8–55.2)	72.5 (60.5–88.2)	78 (61–80)
YMRS	8 (4–19.2)	8 (6–9)	4 (1–8)	8 (6–21)

B) Difference across diagnosis and cluster of pharmacological load			
Clinical score	Diagnosis	Cluster	Diagnosis × cluster
Antipsychotic			F = 8.99, p = 0.003
Mood stabilizers	F = 20.28, p = 0.0002	F = 3.95, p = 0.047	F = 4.73, p = 0.03
Antidepressive	F = 5.95, p = 0.015		
PANSS	F = 5.43, p = 0.02		

C) Correlations between clinical scores and coactivation pattern						
	DISDUR	PANS P	PANS N	PANS G	PANS T	YMRS
BD						
NKG2A + NKp30+	0.13	−0.09	−0.03	−0.25	−0.17	−0.11
NKG2A- NKp30-	0.02	0.18	0.40	0.27	0.38	0.13
SZ						
NKG2A + NKp30+	−0.11	−0.08	−0.05	0.03	0.00	
NKG2A- NKp30-	−0.16	−0.21	0.44	0.37	0.39	

Sigmundsson et al., 2001) were found. Negative symptoms burden was related to cortical thinning in insula (Berthet et al., 2024; Li et al., 2025) and ACC (Bersani et al., 2014) and reduced white matter structural integrity in ATR, inferior fronto-occipital, superior longitudinal fasciculi (Zeng et al., 2016) and cingulum bundle (Hazlett et al., 2011; Hovington et al., 2015). The forceps minor is a commissural white matter tract connecting homologous prefrontal cortical regions across the two hemispheres, whose structural integrity has been associated with efficient interhemispheric communication within frontal networks supporting executive control, attentional regulation, and higher-order emotional regulation (Bauer et al., 2015; Porcu et al., 2024). Taken together, all these findings suggest that shifts in NK cell receptor expression, particularly the loss of double-negative cells and the gain of double-positive cells, may contribute to preserving the integrity of those brain regions and white matter tracts involved in preventing the negative symptoms occurrence.

4.2. A poised NK cells phenotype

Overall, these data suggest that the immunophenotypic signature distinguishing a subset of patients is not solely attributable to NK cell maturation as traditionally defined by CD56bright/dim subsets, but rather to the expression of key functional surface receptors such as

NKp30 and NKG2A. The biological significance of this profile appears particularly relevant in the context of immune surveillance, editing, and tolerance. NKG2A is an inhibitory receptor that binds to HLA-E, a non-classical HLA class I molecule, and is typically associated with less mature, more regulatory NKs. Conversely, NKp30 is a natural cytotoxicity receptor involved in promoting NK cell activation. NKp30 and NKG2A co-expression may define a poised NK cell state, capable of sensing and responding to inflammatory cues, yet restrained by inhibitory signaling, maintaining immune equilibrium. This dynamic is particularly relevant in the interaction between NKs and dendritic cells (DCs). Under physiological conditions, immature DCs with low HLA-E expression may be eliminated by NKs through NKp30-mediated cytotoxicity, a process known as “editing,” which ensures the removal of dysfunctional or tolerogenic DCs. A similar mechanism may occur in NK-T cell interactions, particularly under conditions where NKs detect functional or phenotypic anomalies in activated/dysregulated T cells. In such contexts, NKs may act as regulators of immune homeostasis by selectively eliminating aberrant T cells, thereby preventing excessive or autoreactive immune responses. In this regard, the immune alterations observed in psychiatric patients of the PSI cluster may reflect a different scenario. The co-expression of NKp30 and NKG2A on NKs in PSI patients may not signal dysfunction. Instead, it could represent a balanced, regulatory immune profile that helps control inflammation and

Table 6

Summary of MRI results. A) Percentage of involvement of each tract in the correlation between FA and the frequency of NKs showing double-negativity or double-positivity to NKG2A and NKP30 receptors. B) PSIMIX brain regions showing a reduction of CT compared to HCMIX. C) Summary of brain regions negatively correlated with NKG2A⁻NKP30⁻ considering the whole population. D) Regions positively correlated with NKG2A⁺NKP30⁺, considering only the BD population.

A) Percentage of WM tract affected by correlation between FA and NKG2A and NKP30 coactivation pattern													
	r af	r atr	lcbd	L cbp	r fa	fmi	r ifo	r slf3					
FA negative vs NKG2A ⁻ NKP30 ⁻	7.76	12.7	14.18	6.67	17.64	15.3	13.6	12.5					
FA positive vs NKG2A ⁺ NKP30 ⁺		4.5			7.86	11.5							

B) PSIMIX brain regions showing a reduction of CT compared to HCMIX													
area	p	k	T	x	y	z	Area	p	k	T	x	y	z
L IFG	0	1413	5.6	-52	33	-2	R Precun	0.021	114	4.1	8	-74	49
L SFG	0	1413	4.9	-6	54	34	R LOCx	0	382	5.1	34	-64	47
L FP	0	1413	4.8	-18	42	37	R TOFuCx	0	216	4.8	31	-48	-7
L FP	0.004	156	5.0	-37	50	18	R ParaHyCam	0	216	4.2	24	-33	-18
R SFG	0	1310	5.5	22	28	48	R PreCG	0	678	4.9	43	-5	56
R FP	0	1310	5.1	18	59	16	R PoCG	0	678	4.3	47	-16	53
R IFG	0.001	201	4.1	48	34	6	L PoCG	0.004	153	4.7	-43	-28	64
L SFG	0	259	4.7	-5	12	60	R PreCG	0	386	4.5	40	7	56
R SPL	0.005	149	4.9	30	-55	58	L PreCG	0.008	137	4.4	-43	-7	50
							R PoCG	0	384	4.4	13	-37	77

C) Negative correlation between CT and NKG2A- NKP30- (all patients)													
L insula	0.003				160	5.12		-37		-20			-4
PCC	0.021				114	4.93		-5		-34			28
ACC	0.007				140	4.3		5		28			26
R ParaCing						3.4		13		45			-1

D) Positive correlation between CT and NKG2A+ NKP30+ (BD only)													
L PostCG	0				261	5.6		-55		-23			45
L SMG						4.97		-51		-27			33
L FP	0.033				91	5.52		-26		43			31
R MFG	0.011				114	5.45		32		27			46
R PostCG	0.001				172	5.44		64		-10			28
L IFG	0.006				125	5.38		-46		24			20
L SFG	0.049				83	4.84		-4		45			42
R SMG	0.001				159	4.49		63		-38			22

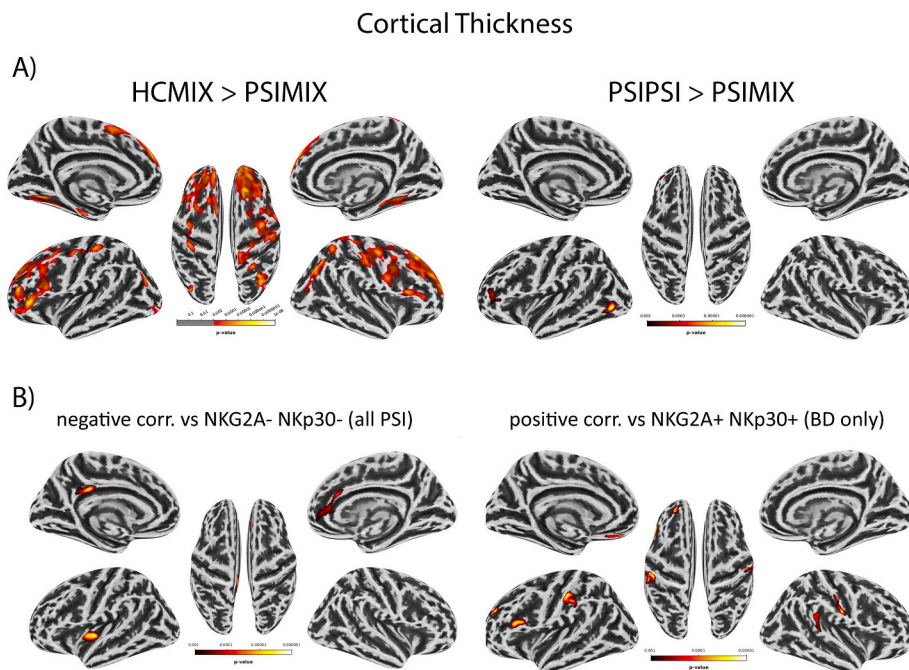


Fig. 4. A) Reduced cortical thickness in PSIMIX compared to HCMIX (left) and PSIPSI (right). B) Correlations between cortical thickness and NKs frequencies. Negative with NKG2A⁻NKP30⁻ cells in all patients (left) and positive with NKG2A⁺NKP30⁺ in BD only (right).

maintain tolerance. This specific NK cell signature might be a protective adaptation, preserving immune responsiveness while preventing over-activation. This interpretation is supported by the fact that PSI patients with this NK profile show more favorable clinical outcomes, suggesting the signature is linked to beneficial immunoregulation rather than harmful inflammation. The reduction of double-negative NKs supports the hypothesis of a selective expansion or recruitment of NK subsets actively engaged in a regulatory loop relevant to disease resilience or vulnerability. Interestingly, clustering analysis grouped typically developing (HC) individuals with patients exhibiting greater white matter damage (PSIMIX), suggesting that traditional diagnostic categories may conceal underlying biological heterogeneity. One possible interpretation is that some HC individuals share immune profiles with patients at higher risk for subclinical pathology, warranting further longitudinal investigation.

5. Limitations

The present study needs to be considered in the light of the following limitations/shortcomings. We did not observe a direct correlation between structural brain alterations and the severity of negative symptoms, but only with the frequency of specific NK cell populations. However, several studies reporting associations between structural changes and symptom severity followed a similar approach – either by selecting participants with stable negative symptom profiles or by identifying subgroups through clustering where negative symptoms predominated. Moreover, for the cross-sectional design of our study, we cannot establish a causal relationship between NK cell receptor profiles and structural brain alterations, but rather an association, although strong and deeply grounded in the present literature. Although the number of patients who underwent MRI is limited, the brain regions and white matter tracts identified align closely with those consistently implicated in the literature in relation to negative symptom burden, supporting the reliability of our findings. Metabolic and cardiovascular comorbidities commonly associated with schizophrenia and bipolar disorder, including obesity, diabetes, and hypertension, may contribute to structural brain alterations and potentially influence neuroimmune measures. Although subjects with major medical and inflammatory conditions were excluded according to the study exclusion criteria, detailed metabolic data were not systematically available for all participants and therefore could not be included as covariates in the present analyses. The present sample was recruited in a single tertiary academic psychiatric center and mainly included acutely ill hospitalized Caucasian patients. Therefore, the findings may not be fully generalizable to community-based, outpatient, clinically stable, or ethnically more heterogeneous populations with schizophrenia or bipolar disorder.

6. Conclusions

These findings highlight the potential of deep immunophenotyping in uncovering novel immune signatures within psychiatric populations. The specific NK cell profile defined by NKp30 and NKG2A co-expression may represent a biologically and clinically relevant marker of immune regulation, neuroprotection, and disease heterogeneity. Future studies should explore whether this phenotype may serve as a biomarker or a therapeutic target to modulate neuroimmune interactions in selected patient subgroups.

CRediT authorship contribution statement

Alberto Inuggi: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation. **Tiziana Altosole:** Investigation, Formal analysis, Data curation. **Andrea Escelsior:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Investigation, Conceptualization. **Laura Damente:** Investigation, Formal analysis, Data curation. **Elisa Cilia:** Writing –

original draft, Investigation. **Luca Favilla:** Investigation. **Giacomo Marengo:** Investigation. **Bruno Sterlini:** Writing – review & editing, Resources, Conceptualization. **Chiara Rosa Maria Uras:** Writing – review & editing. **Barbara Parisi:** Writing – review & editing. **Riccardo Guglielmo:** Writing – review & editing. **Beatriz Pereira Da Silva:** Resources. **Fabrizio Loiacono:** Writing – review & editing, Resources. **Daniela Fenoglio:** Writing – review & editing, Supervision. **Gilberto Filaci:** Writing – review & editing, Supervision. **Mario Amore:** Writing – review & editing, Project administration. **Gianluca Serafini:** Writing – review & editing, Project administration. **Emanuela Marcenaro:** Writing – review & editing, Writing – original draft, Methodology.

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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.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jad.2026.122178>.

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