

## Reporting Summary

Nature Portfolio wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Portfolio policies, see our [Editorial Policies](#) and the [Editorial Policy Checklist](#).

### Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a Confirmed

- ☐ ☒ The exact sample size ( $n$ ) for each experimental group/condition, given as a discrete number and unit of measurement
- ☐ ☒ A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
- ☐ ☒ The statistical test(s) used AND whether they are one- or two-sided  
*Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
- ☒ ☐ A description of all covariates tested
- ☒ ☐ A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
- ☐ ☒ A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
- ☐ ☒ For null hypothesis testing, the test statistic (e.g.  $F$ ,  $t$ ,  $r$ ) with confidence intervals, effect sizes, degrees of freedom and  $P$  value noted  
*Give  $P$  values as exact values whenever suitable.*
- ☒ ☐ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
- ☒ ☐ For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
- ☒ ☐ Estimates of effect sizes (e.g. Cohen's  $d$ , Pearson's  $r$ ), indicating how they were calculated

*Our web collection on [statistics for biologists](#) contains articles on many of the points above.*

### Software and code

Policy information about [availability of computer code](#)

|                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Data collection | Single Cell Sequencing: 10X Chromium Single Cell V(D)J Reagent Kits (v1.1), sequenced on Novaseq 6000 (Illumina)<br>Flow Cytometry: Samples were acquired using BD FACSLyrics device and BD FACS Suite (v1.5)                                                                                                                                                                                                                                                                                                                                                                      |
| Data analysis   | Flow Cytometry: FlowJo v10.6.2<br>Single Cell Sequencing: Alignment with cellranger v6.1.2, data normalization and transformation using SCTransform from Seurat (v4.3.0)<br>General data analysis were done in R (v4.2.3) or Python (v3.9.16), with tidyverse (v2.0.0) or numpy (v1.24.3) or pandas (v2.0.2).<br>All additional softwares and packages used are detailed in the Methods sections including: arcasHLA (v0.5.0), TRUST4 (v1.0.9), scikit-learn (v1.2.2), scikit-optimize (v0.9.0), shap (v0.41.0), GSVA (v1.46.0), pROC (v1.18.2), caret (v6.0-94), xgboost (v1.7.4) |

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio [guidelines for submitting code & software](#) for further information.

## Data

Policy information about [availability of data](#)

All manuscripts must include a [data availability statement](#). This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our [policy](#)

Single cell sequencing data for BT21 have been deposited in NCBI BioProject with accession code PRJNA985415. External datasets were obtained from GSE123139, GSE173351 and phs002748.v1.p1.

## Human research participants

Policy information about [studies involving human research participants and Sex and Gender in Research](#).

|                             |                                                                                                                                                                                                                       |
|-----------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Reporting on sex and gender | The BT21 cell line was derived from a male patient. The sex of patients from external datasets is reported in each respective paper.                                                                                  |
| Population characteristics  | 62 year old male patient with a brain metastasis of a previously diagnosed with melanoma.                                                                                                                             |
| Recruitment                 | The patient was recruited in University Hospital Mannheim and provided written consent. We were able to obtain very fresh resection material which contributed to our successful establishment of the BT21 cell line. |
| Ethics oversight            | Study was approved by the institutional review board (Ethikkommission 2019-643N)                                                                                                                                      |

Note that full information on the approval of the study protocol must also be provided in the manuscript.

## Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see [nature.com/documents/nr-reporting-summary-flat.pdf](https://nature.com/documents/nr-reporting-summary-flat.pdf)

## Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

|                 |                                                                                                                                                                                                                                                                                                       |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Sample size     | No sample size calculation was performed. The most frequent TCRs were chosen for model training, and the number of TCRs tested for a single sample is of a similar size or larger than in previous studies. The validation sample size was based on data availability of publicly available datasets. |
| Data exclusions | Low quality single cells are excluded from further analysis as described in Methods for failing to meet quality control thresholds. External datasets where no TCR validation done were excluded and patients with either only reactive or non-reactive TCR were omitted.                             |
| Replication     | The microwell data in Extended Data Figures 5 and 6 replicates the reactivity testing data in Fig.1, confirming reactivity of these TCRs against the BT21 cell line.                                                                                                                                  |
| Randomization   | Random train/test set splits were used when training models in order to evaluate them, as common practice.                                                                                                                                                                                            |
| Blinding        | The investigators performing the experimental TCR testing analyses (FACS, Cellply) were blinded as to the expected reactivity of TCRs tested.                                                                                                                                                         |

## Behavioural & social sciences study design

All studies must disclose on these points even when the disclosure is negative.

|                   |                                                                                                                                                                                                 |
|-------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Study description | Briefly describe the study type including whether data are quantitative, qualitative, or mixed-methods (e.g. qualitative cross-sectional, quantitative experimental, mixed-methods case study). |
| Research sample   | State the research sample (e.g. Harvard university undergraduates, villagers in rural India) and provide relevant demographic                                                                   |

|                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|-------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Research sample   | <i>information (e.g. age, sex) and indicate whether the sample is representative. Provide a rationale for the study sample chosen. For studies involving existing datasets, please describe the dataset and source.</i>                                                                                                                                                                                                                                                                |
| Sampling strategy | <i>Describe the sampling procedure (e.g. random, snowball, stratified, convenience). Describe the statistical methods that were used to predetermine sample size OR if no sample-size calculation was performed, describe how sample sizes were chosen and provide a rationale for why these sample sizes are sufficient. For qualitative data, please indicate whether data saturation was considered, and what criteria were used to decide that no further sampling was needed.</i> |
| Data collection   | <i>Provide details about the data collection procedure, including the instruments or devices used to record the data (e.g. pen and paper, computer, eye tracker, video or audio equipment) whether anyone was present besides the participant(s) and the researcher, and whether the researcher was blind to experimental condition and/or the study hypothesis during data collection.</i>                                                                                            |
| Timing            | <i>Indicate the start and stop dates of data collection. If there is a gap between collection periods, state the dates for each sample cohort.</i>                                                                                                                                                                                                                                                                                                                                     |
| Data exclusions   | <i>If no data were excluded from the analyses, state so OR if data were excluded, provide the exact number of exclusions and the rationale behind them, indicating whether exclusion criteria were pre-established.</i>                                                                                                                                                                                                                                                                |
| Non-participation | <i>State how many participants dropped out/declined participation and the reason(s) given OR provide response rate OR state that no participants dropped out/declined participation.</i>                                                                                                                                                                                                                                                                                               |
| Randomization     | <i>If participants were not allocated into experimental groups, state so OR describe how participants were allocated to groups, and if allocation was not random, describe how covariates were controlled.</i>                                                                                                                                                                                                                                                                         |

## Ecological, evolutionary & environmental sciences study design

All studies must disclose on these points even when the disclosure is negative.

|                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|--------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Study description        | <i>Briefly describe the study. For quantitative data include treatment factors and interactions, design structure (e.g. factorial, nested, hierarchical), nature and number of experimental units and replicates.</i>                                                                                                                                                                                                                                         |
| Research sample          | <i>Describe the research sample (e.g. a group of tagged <i>Passer domesticus</i>, all <i>Stenocereus thurberi</i> within Organ Pipe Cactus National Monument), and provide a rationale for the sample choice. When relevant, describe the organism taxa, source, sex, age range and any manipulations. State what population the sample is meant to represent when applicable. For studies involving existing datasets, describe the data and its source.</i> |
| Sampling strategy        | <i>Note the sampling procedure. Describe the statistical methods that were used to predetermine sample size OR if no sample-size calculation was performed, describe how sample sizes were chosen and provide a rationale for why these sample sizes are sufficient.</i>                                                                                                                                                                                      |
| Data collection          | <i>Describe the data collection procedure, including who recorded the data and how.</i>                                                                                                                                                                                                                                                                                                                                                                       |
| Timing and spatial scale | <i>Indicate the start and stop dates of data collection, noting the frequency and periodicity of sampling and providing a rationale for these choices. If there is a gap between collection periods, state the dates for each sample cohort. Specify the spatial scale from which the data are taken</i>                                                                                                                                                      |
| Data exclusions          | <i>If no data were excluded from the analyses, state so OR if data were excluded, describe the exclusions and the rationale behind them, indicating whether exclusion criteria were pre-established.</i>                                                                                                                                                                                                                                                      |
| Reproducibility          | <i>Describe the measures taken to verify the reproducibility of experimental findings. For each experiment, note whether any attempts to repeat the experiment failed OR state that all attempts to repeat the experiment were successful.</i>                                                                                                                                                                                                                |
| Randomization            | <i>Describe how samples/organisms/participants were allocated into groups. If allocation was not random, describe how covariates were controlled. If this is not relevant to your study, explain why.</i>                                                                                                                                                                                                                                                     |
| Blinding                 | <i>Describe the extent of blinding used during data acquisition and analysis. If blinding was not possible, describe why OR explain why blinding was not relevant to your study.</i>                                                                                                                                                                                                                                                                          |

Did the study involve field work? ☐ Yes ☐ No

## Field work, collection and transport

|                        |                                                                                                                                               |
|------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------|
| Field conditions       | <i>Describe the study conditions for field work, providing relevant parameters (e.g. temperature, rainfall).</i>                              |
| Location               | <i>State the location of the sampling or experiment, providing relevant parameters (e.g. latitude and longitude, elevation, water depth).</i> |
| Access & import/export | <i>Describe the efforts you have made to access habitats and to collect and import/export your samples in a responsible manner and in</i>     |

|                        |                                                                                                                                                                                             |
|------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Access & import/export | compliance with local, national and international laws, noting any permits that were obtained (give the name of the issuing authority, the date of issue, and any identifying information). |
| Disturbance            | Describe any disturbance caused by the study and how it was minimized.                                                                                                                      |

## Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

### Materials & experimental systems

| n/a                                 | Involved in the study                                     |
|-------------------------------------|-----------------------------------------------------------|
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> Antibodies            |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> Eukaryotic cell lines |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Palaeontology and archaeology    |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Animals and other organisms      |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Clinical data                    |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Dual use research of concern     |

### Methods

| n/a                                 | Involved in the study                              |
|-------------------------------------|----------------------------------------------------|
| <input checked="" type="checkbox"/> | <input type="checkbox"/> ChIP-seq                  |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> Flow cytometry |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> MRI-based neuroimaging    |

## Antibodies

|                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Antibodies used | anti-CD3-BV510 (BD, cat 564713, clone HIT3A), anti-mTCRbeta-PE (BioLegend UK, cat 109208, clone H57-597), anti-CD107a-APC-H7 (BD, cat 561343, clone H4A3), anti-TNF-alpha-BV711 (Biolegend, cat 502940, clone MAb11), anti-Melan A-FITC (Santa Cruz Technology, cat sc-20032, clone A103)                                                                                                                                                                                        |
| Validation      | All antibodies were used according to manufacturer's instruction or titrated prior to use (dilutions listed in paper methods section).<br>anti-CD3-BV510: Manufacturer's quality tested for flow cytometry<br>anti-mTCRbeta-PE: Manufacturer's quality tested for flow cytometry<br>anti-CD107a-APC-H7: Manufacturer's quality tested for intracellular flow cytometry staining<br>anti-TNF-alpha-BV711: Manufacturer's quality tested for intracellular flow cytometry staining |

## Eukaryotic cell lines

Policy information about [cell lines and Sex and Gender in Research](#)

|                                                                      |                                                                          |
|----------------------------------------------------------------------|--------------------------------------------------------------------------|
| Cell line source(s)                                                  | BT21: a cell line derived in-house from a male patient                   |
| Authentication                                                       | Exome-sequencing was done tumor material and the BT21 cell line material |
| Mycoplasma contamination                                             | All cell lines tested negative for mycoplasma contamination              |
| Commonly misidentified lines<br>(See <a href="#">ICLAC</a> register) | No commonly misidentified cell lines were used in this study             |

## Palaeontology and Archaeology

|                                                                                                                                                 |                                                                                                                                                                                                                                                                               |
|-------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Specimen provenance                                                                                                                             | Provide provenance information for specimens and describe permits that were obtained for the work (including the name of the issuing authority, the date of issue, and any identifying information). Permits should encompass collection and, where applicable, export.       |
| Specimen deposition                                                                                                                             | Indicate where the specimens have been deposited to permit free access by other researchers.                                                                                                                                                                                  |
| Dating methods                                                                                                                                  | If new dates are provided, describe how they were obtained (e.g. collection, storage, sample pretreatment and measurement), where they were obtained (i.e. lab name), the calibration program and the protocol for quality assurance OR state that no new dates are provided. |
| <input type="checkbox"/> Tick this box to confirm that the raw and calibrated dates are available in the paper or in Supplementary Information. |                                                                                                                                                                                                                                                                               |
| Ethics oversight                                                                                                                                | Identify the organization(s) that approved or provided guidance on the study protocol, OR state that no ethical approval or guidance was required and explain why not.                                                                                                        |

Note that full information on the approval of the study protocol must also be provided in the manuscript.

## Animals and other research organisms

Policy information about [studies involving animals](#); ARRIVE [guidelines](#) recommended for reporting animal research, and [Sex and Gender in Research](#)

|                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|-------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Laboratory animals      | <i>For laboratory animals, report species, strain and age OR state that the study did not involve laboratory animals.</i>                                                                                                                                                                                                                                                                                                                                      |
| Wild animals            | <i>Provide details on animals observed in or captured in the field; report species and age where possible. Describe how animals were caught and transported and what happened to captive animals after the study (if killed, explain why and describe method; if released, say where and when) OR state that the study did not involve wild animals.</i>                                                                                                       |
| Reporting on sex        | <i>Indicate if findings apply to only one sex; describe whether sex was considered in study design, methods used for assigning sex. Provide data disaggregated for sex where this information has been collected in the source data as appropriate; provide overall numbers in this Reporting Summary. Please state if this information has not been collected. Report sex-based analyses where performed, justify reasons for lack of sex-based analysis.</i> |
| Field-collected samples | <i>For laboratory work with field-collected samples, describe all relevant parameters such as housing, maintenance, temperature, photoperiod and end-of-experiment protocol OR state that the study did not involve samples collected from the field.</i>                                                                                                                                                                                                      |
| Ethics oversight        | <i>Identify the organization(s) that approved or provided guidance on the study protocol, OR state that no ethical approval or guidance was required and explain why not.</i>                                                                                                                                                                                                                                                                                  |

Note that full information on the approval of the study protocol must also be provided in the manuscript.

## Clinical data

Policy information about [clinical studies](#)

All manuscripts should comply with the ICMJE [guidelines for publication of clinical research](#) and a completed [CONSORT checklist](#) must be included with all submissions.

|                             |                                                                                                                          |
|-----------------------------|--------------------------------------------------------------------------------------------------------------------------|
| Clinical trial registration | <i>Provide the trial registration number from ClinicalTrials.gov or an equivalent agency.</i>                            |
| Study protocol              | <i>Note where the full trial protocol can be accessed OR if not available, explain why.</i>                              |
| Data collection             | <i>Describe the settings and locales of data collection, noting the time periods of recruitment and data collection.</i> |
| Outcomes                    | <i>Describe how you pre-defined primary and secondary outcome measures and how you assessed these measures.</i>          |

## Dual use research of concern

Policy information about [dual use research of concern](#)

### Hazards

Could the accidental, deliberate or reckless misuse of agents or technologies generated in the work, or the application of information presented in the manuscript, pose a threat to:

| No                                  | Yes                                                 |
|-------------------------------------|-----------------------------------------------------|
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Public health              |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> National security          |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Crops and/or livestock     |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Ecosystems                 |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Any other significant area |

## Experiments of concern

Does the work involve any of these experiments of concern:

- | No                                  | Yes                      |                                                                             |
|-------------------------------------|--------------------------|-----------------------------------------------------------------------------|
| <input checked="" type="checkbox"/> | <input type="checkbox"/> | Demonstrate how to render a vaccine ineffective                             |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> | Confer resistance to therapeutically useful antibiotics or antiviral agents |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> | Enhance the virulence of a pathogen or render a nonpathogen virulent        |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> | Increase transmissibility of a pathogen                                     |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> | Alter the host range of a pathogen                                          |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> | Enable evasion of diagnostic/detection modalities                           |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> | Enable the weaponization of a biological agent or toxin                     |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> | Any other potentially harmful combination of experiments and agents         |

## ChIP-seq

### Data deposition

- ☐ Confirm that both raw and final processed data have been deposited in a public database such as [GEO](#).
- ☐ Confirm that you have deposited or provided access to graph files (e.g. BED files) for the called peaks.

#### Data access links

May remain private before publication.

For "Initial submission" or "Revised version" documents, provide reviewer access links. For your "Final submission" document, provide a link to the deposited data.

#### Files in database submission

Provide a list of all files available in the database submission.

#### Genome browser session

(e.g. [UCSC](#))

Provide a link to an anonymized genome browser session for "Initial submission" and "Revised version" documents only, to enable peer review. Write "no longer applicable" for "Final submission" documents.

## Methodology

#### Replicates

Describe the experimental replicates, specifying number, type and replicate agreement.

#### Sequencing depth

Describe the sequencing depth for each experiment, providing the total number of reads, uniquely mapped reads, length of reads and whether they were paired- or single-end.

#### Antibodies

Describe the antibodies used for the ChIP-seq experiments; as applicable, provide supplier name, catalog number, clone name, and lot number.

#### Peak calling parameters

Specify the command line program and parameters used for read mapping and peak calling, including the ChIP, control and index files used.

#### Data quality

Describe the methods used to ensure data quality in full detail, including how many peaks are at FDR 5% and above 5-fold enrichment.

#### Software

Describe the software used to collect and analyze the ChIP-seq data. For custom code that has been deposited into a community repository, provide accession details.

## Flow Cytometry

### Plots

Confirm that:

- ☒ The axis labels state the marker and fluorochrome used (e.g. CD4-FITC).
- ☒ The axis scales are clearly visible. Include numbers along axes only for bottom left plot of group (a 'group' is an analysis of identical markers).
- ☒ All plots are contour plots with outliers or pseudocolor plots.
- ☒ A numerical value for number of cells or percentage (with statistics) is provided.

### Methodology

#### Sample preparation

TCR-encoding RNA was electroporated into expanded healthy donor PBMCs using the Lonza 4D nucleofactor (program EO-115, solution P3 supplemented according to the manufacturer's recommendations), which were plated into 48-well plates containing TexMACS media (Miltenyi 130-097-196) supplemented with 2% human AB serum.

18-24 hours after electroporation, cells were harvested and 50 IU/mL benzonase (Speed BioSystems YCP1200-50KU) were

added to avoid cell clumping. TCR expression levels were measured via flow cytometry with markers including fixable viability dye (AF700, BD), CD3 (clone HIT3A, BV510, BD), CD4 (clone SK3, BV786, BD), CD8 (clone RPA-T8, PerCP-Cy5.5, Invitrogen) and mTCRb (clone H57-597, PE, Biolegend).

To assess TCR reactivity, a total of 150,000 T cells and 75,000 cells of the patient-autologous tumor cell line were co-cultured in U-bottom 96-well plates in a total volume of 200  $\mu$ L. Wells with only T cells, or T cells and TransAct beads (Miltenyi 130-111-160), were used as negative and positive controls, respectively. 5  $\mu$ L of CD107a FACS antibody (BD, REF 561343) was added per well. After one hour of co-culture, GolgiPlug and GolgiStop (BD 555029 and 554724) were added to reach a 1:1000 dilution, and after four additional hours of co-culture cells were used for flow cytometry analysis.

Markers included fixable viability dye (AF700, eBioscience), CD3 (clone HIT3A, BV510, BD), CD4 (clone SK3, APC, BD), CD8 (clone RPA-T8, PerCP-Cy5.5, Invitrogen), mTCRb (clone H57-597, PE, Biolegend) and TNFa (clone MAb11, BV711, Biolegend). Samples were acquired on a FACS Lyric device, flow cytometry data was analysed using FlowJo software, v10.6.2 (FlowJo LLC).

|                           |                                                                                                                                                                                     |
|---------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Instrument                | BD FACSLyrics, ZE5 Cell Analyzer                                                                                                                                                    |
| Software                  | BD FACS Suite (v1.5), FlowJo (v10.6.2)                                                                                                                                              |
| Cell population abundance | Population abundance varies by TCR tested: the maximum amount of reactive (CD107a+) cells is 33%, ranging down to 0% for non-reactive TCRs. See example in Extended Data Figure 3b. |
| Gating strategy           | Gated on lymphocytes based on size and granularity (FSC vs SSC) -> singlet -> live cells (negative on LIVE/DEAD) -> CD3+ -> mTCRb+ -> CD107a+ (Extended Data Figure 3a)             |

☒ Tick this box to confirm that a figure exemplifying the gating strategy is provided in the Supplementary Information.

## Magnetic resonance imaging

### Experimental design

|                                 |                                                                                                                                                                                                                                                            |
|---------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Design type                     | Indicate task or resting state; event-related or block design.                                                                                                                                                                                             |
| Design specifications           | Specify the number of blocks, trials or experimental units per session and/or subject, and specify the length of each trial or block (if trials are blocked) and interval between trials.                                                                  |
| Behavioral performance measures | State number and/or type of variables recorded (e.g. correct button press, response time) and what statistics were used to establish that the subjects were performing the task as expected (e.g. mean, range, and/or standard deviation across subjects). |

### Acquisition

|                               |                                                                                                                                                                                    |
|-------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Imaging type(s)               | Specify: functional, structural, diffusion, perfusion.                                                                                                                             |
| Field strength                | Specify in Tesla                                                                                                                                                                   |
| Sequence & imaging parameters | Specify the pulse sequence type (gradient echo, spin echo, etc.), imaging type (EPI, spiral, etc.), field of view, matrix size, slice thickness, orientation and TE/TR/flip angle. |
| Area of acquisition           | State whether a whole brain scan was used OR define the area of acquisition, describing how the region was determined.                                                             |
| Diffusion MRI                 | <input type="checkbox"/> Used <input type="checkbox"/> Not used                                                                                                                    |

### Preprocessing

|                            |                                                                                                                                                                                                                                         |
|----------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Preprocessing software     | Provide detail on software version and revision number and on specific parameters (model/functions, brain extraction, segmentation, smoothing kernel size, etc.).                                                                       |
| Normalization              | If data were normalized/standardized, describe the approach(es): specify linear or non-linear and define image types used for transformation OR indicate that data were not normalized and explain rationale for lack of normalization. |
| Normalization template     | Describe the template used for normalization/transformation, specifying subject space or group standardized space (e.g. original Talairach, MNI305, ICBM152) OR indicate that the data were not normalized.                             |
| Noise and artifact removal | Describe your procedure(s) for artifact and structured noise removal, specifying motion parameters, tissue signals and physiological signals (heart rate, respiration).                                                                 |
| Volume censoring           | Define your software and/or method and criteria for volume censoring, and state the extent of such censoring.                                                                                                                           |

### Statistical modeling & inference

|                         |                                                                                                                                                                                                                  |
|-------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Model type and settings | Specify type (mass univariate, multivariate, RSA, predictive, etc.) and describe essential details of the model at the first and second levels (e.g. fixed, random or mixed effects; drift or auto-correlation). |
|-------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|



Effect(s) tested

Define precise effect in terms of the task or stimulus conditions instead of psychological concepts and indicate whether ANOVA or factorial designs were used.

Specify type of analysis: ☐ Whole brain ☐ ROI-based ☐ BothStatistic type for inference  
(See [Eklund et al. 2016](#))

Specify voxel-wise or cluster-wise and report all relevant parameters for cluster-wise methods.

Correction

Describe the type of correction and how it is obtained for multiple comparisons (e.g. FWE, FDR, permutation or Monte Carlo).

## Models & analysis

n/a | Involved in the study

- ☐ ☐ Functional and/or effective connectivity
- ☐ ☐ Graph analysis
- ☐ ☐ Multivariate modeling or predictive analysis

Functional and/or effective connectivity

Report the measures of dependence used and the model details (e.g. Pearson correlation, partial correlation, mutual information).

Graph analysis

Report the dependent variable and connectivity measure, specifying weighted graph or binarized graph, subject- or group-level, and the global and/or node summaries used (e.g. clustering coefficient, efficiency, etc.).

Multivariate modeling and predictive analysis

Specify independent variables, features extraction and dimension reduction, model, training and evaluation metrics.