

Reproducible brain-wide association studies do not necessarily require thousands of individuals

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In brain-wide association studies (BWAS), researchers correlate behavior with the inter-individual variability in functional or structural properties of distinct brain regions. Marek, Tervo-Clemmens, and colleagues¹ (hereinafter, M&TC) empirically assess statistical power, replication rate, type I error, sign error, and effect size inflation in BWAS using data from three large-scale neuroimaging initiatives (i.e., ABCD², Human Connectome Project³ - HCP -, and UK Biobank⁴). Their results indicate that reproducible brain-behavior associations require thousands of observations. Here, leveraging synthetic and HCP data, we demonstrate that their calculations overestimate the sample size needed to detect reproducible effects by one order of magnitude.

In their article, M&TC assess the reproducibility of BWAS by randomly resampling (1,000 bootstraps) participants at increasing sample sizes (ranging from 25 to ~4,000). The correlation between brain features (e.g., cortical thickness) and behavior (e.g., cognitive ability) is computed at each sample size, allowing the empirical evaluation of power, type I error, sign error (i.e., type S error), inflation rate (i.e., type M error), and probability of replication as a function of the number of observations.

Their findings indicate that thousands of individuals are required for BWAS to detect true effects reliably. In addition, M&TC analyses reveal that studies on hundreds of participants - the typical size of BWAS - fail to replicate, produce inflated effect sizes, or even opposite sign associations (e.g., negative association when the actual correlation is positive).

We have read with great interest the M&TC article and value the authors' effort to perform billions of analyses and test BWAS reproducibility; however, we believe that their conclusions are based on a statistical procedure that biases sample size estimates and disregards region-specific effects: the averaging of metrics (e.g., power, replication rate) across brain parcels. Here, using synthetic and HCP data, we show that small effect sizes can be reliably detected with less than a thousand individuals when metrics are computed at a single region level.

To illustrate the M&TC procedure and the issue with sample size calculation, we take the estimate of statistical power as an example (Figure 1A). Features of 4 distinct brain regions (ROIs) significantly correlate with behavior in the full sample. Importantly, each ROI demonstrates a specific effect size (i.e., Pearson's correlation), ranging from $r = 0.05$ (Figure 1A,

blue ROI) to $r = 0.20$ (orange ROI). Following the M&TC procedure, random resamplings are performed at multiple sample sizes (we show hypothetical $n = 375$ in Figure 1A). For each significant ROI in the full sample, power is computed as the percentage of random resamplings passing the same statistical threshold and then averaged across regions (line 53 in the function `abcd_statisticalerrors.m` made available by the authors; Figure 3D of the original article). Yet, the introduction of this last step produces a biased estimate of statistical power and sample size, which refers to a hypothetical effect size not even measured across the four significant regions. The bias introduced by the averaging procedure penalizes larger effects (i.e., they are deemed to require larger samples to be detected; orange and purple ROIs in the example), whereas smaller effects (i.e., blue and green ROIs) are - paradoxically - favored. As detailed below, this consideration holds for other metrics (e.g., type M and type S errors), brain features (e.g., thickness, connectivity), and levels of anatomical resolution (e.g., components, networks, ROIs, edges/vertices) reported in the original article.

We argue that, rather than average metrics, region-specific estimates should be preferred when assessing BWAS reproducibility and substantiate our claim by simulating and analyzing brain-behavior associations like those reported in the original M&TC article (source data Figure 1).

To this aim, firstly, we simulate cognitive ability data and 100 resting-state functional connectivity (rsFC) components for 3,604 participants (i.e., the full sample in the rsFC dataset of M&TC; function `generate_simulated_data.m`; MATLAB® code available at <https://github.com/giacomohandjaras/BWAS/>). The distribution of correlation values obtained for the 100 simulated rsFC components and synthetic cognitive ability scores (Figure 1B, left panel) well approximates (tolerance: $r \pm 1e-4$) values reported in M&TC (Figure 1B, left panel of the original article). Using a bootstrapping procedure (`bootstrap_correlation.m`), we then obtain 1,000 random resamplings of brain data and behavioral scores at increasing sample sizes (from $n = 25$ to $n = 3,000$), as in the original report. We characterize sampling variability for the strongest association among the 100 correlations ($r = 0.1652$; Figure 1B, right panel; see Figure 1F of the original M&TC article for comparison) and assess power, replication rate, and statistical errors after controlling for the number of tests ($q < 0.05$ FDR corrected⁵).

For each reference rsFC component identified in the full sample ($q < 0.05$), we compute statistical power at multiple sample sizes as the percentage of random resamplings passing the same statistical threshold (`compute_power.m`). To assess type M error, we compute the ratio between the correlation value obtained for each significant resampling and the one obtained in the full sample. The inflation percentage is then estimated at each sample size as the average across resamplings (`compute_type_m_alternative.m`). Also, type S error is calculated as the percentage of resamplings in which the brain-behavior correlation has opposite sign compared to the one measured in the full sample. The calculation of type S error is repeated for unthresholded and FDR-corrected correlations (`compute_type_s.m`). For the probability of replication, instead, we split the simulated dataset into discovery and replication sets of equal size ($n = 1,802$). The

percentage of successful replication is computed for each simulated rsFC component and sample size as the proportion of resamplings yielding a significant brain-behavior correlation in both the discovery and replication sets (*compute_replication.m*). Crucially, to demonstrate how aggregated metrics produce biased estimates of BWAS reproducibility, we average across rsFC components, power, type M error, type S error, and replication rates (as in M&TC). We report and visualize averaged as well as region-specific metrics.

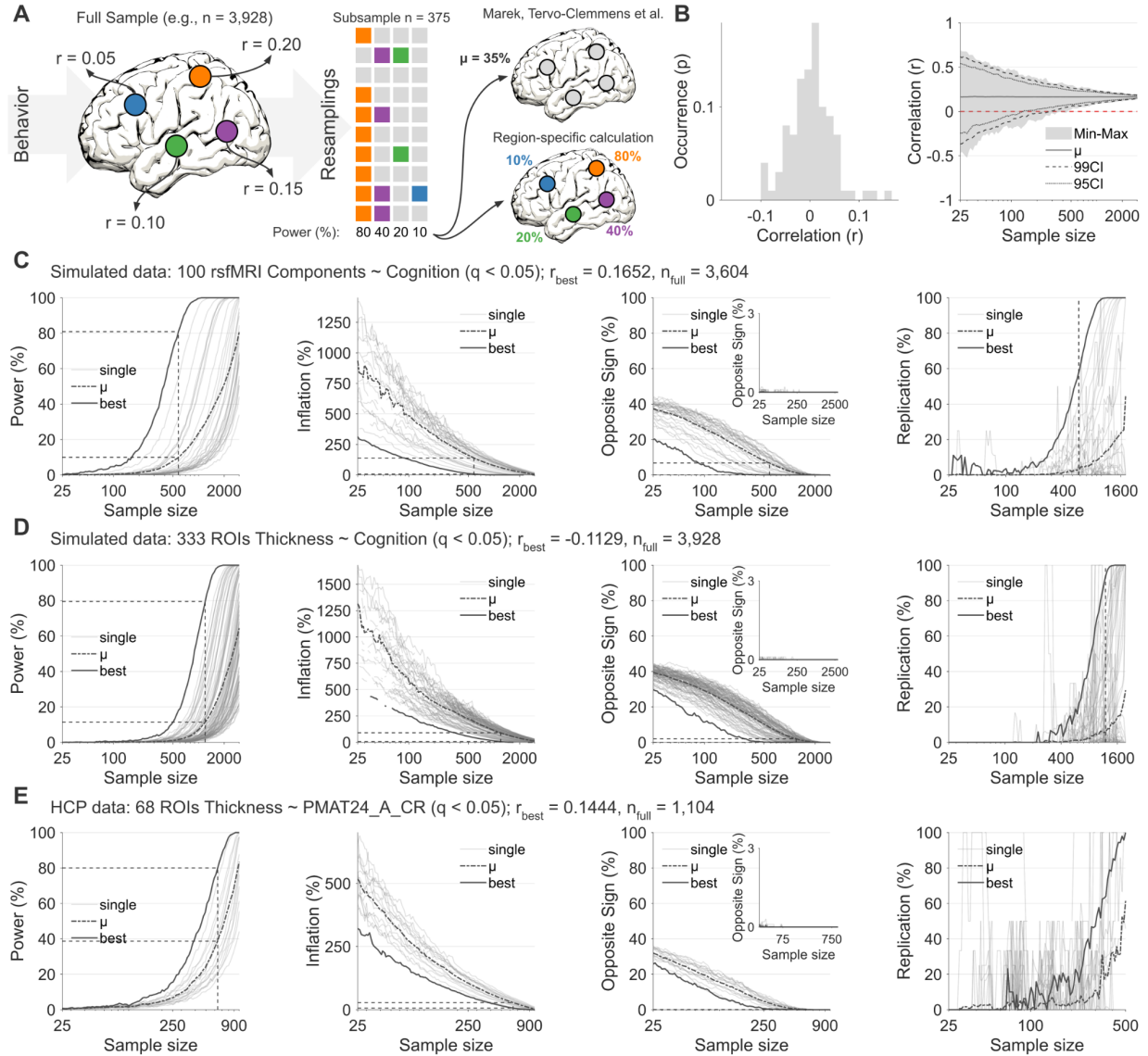


Figure 1. Panel A illustrates the analytical pipeline adopted by M&TC to assess the reproducibility of BWAS, as well as the region-specific calculation we propose. Statistical power is computed at multiple sample sizes for ROIs passing the statistical significance in the full sample (orange, purple, green, and blue regions; $n = 3,928$). Afterward, the authors compute the average power across significant ROIs. We suggest an alternative region-specific power calculation and test the reliability of the two methods across simulated and Human Connectome Project (HCP) data. In B, we show the distribution of synthetic correlations for the rsFC components vs. cognitive ability (left panel). Correlations are generated starting from source data in Figure 1 of the original M&TC article. To ease the

comparison between our simulated and original M&TC data, we also report the sampling variability for the largest simulated correlation ($r = 0.1652$, right panel; Figure 1F in M&TC). In **C**, **D**, and **E**, we report statistical power, effect size inflation (type M error), percentage of opposite sign correlations (type S error; unthresholded: larger plot; thresholded: insert plot), and replication rate as a function of sample size. Metrics are computed on simulated (panel **C**: rsFC components vs. cognitive ability; panel **D**: ROI thickness vs. cognitive ability) and real data (panel **E**: HCP ROI thickness vs. fluid intelligence) after applying the false discovery rate correction for multiple comparisons ($q < 0.05$). In each plot, the dotted line represents the average across regions (as in M&TC), the dark solid line refers to the brain parcel showing the best correlation, whereas the solid gray lines represent all other regions passing the statistical threshold in the full sample. Where present, dashed lines indicate the sample size required for 80% power based on the region-specific calculation. We draw dashed projection lines crossing the average metric at the same sample size to highlight the difference between the M&TC method and the one proposed here.

As in the original article, the strongest association between simulated rsFC components and cognition in the full sample ($n = 3,604$) is $r = 0.1652$ (*simulation_parent_script.m*). For this correlation, 80% power is reached at $n = 580$ after controlling for multiple comparisons ($q < 0.05$; Figure 1C, solid black line). Also, at $n = 580$, the percentage of inflation is 7%, there is a 0% probability of observing opposite sign correlations for both unthresholded, and FDR corrected data, and the replication rate is 59%. Importantly, in addition to the best simulated rsFC component, other associations attain 80% power with $n \leq 1,000$ ($q < 0.05$; Figure 1C, solid grey lines), and most of these correlations reach a 90% replication rate with $n \approx 1,500$. Conversely, the average statistical power computed across rsFC components is 10% at $n = 580$ ($q < 0.05$; Figure 1C, dotted line). Also, for the same sample size, the average inflation is 139%, there is a 7% probability of observing opposite sign correlations across rsFC components, and the average replication rate is 3%. These biased estimates obtained from simulated data are in line with those documented in the original M&TC article, where - using real data - the authors indicate a 5% replication rate for BWAS with $n < 500$ (pg. 657) and only 68% power at $n \approx 4,000$.

To ensure that the discrepancies between region-specific and average metrics are not due to the distribution of correlations observed for rsFC components, we repeat all analyses on simulated ROI-based cortical thickness values (333 ROIs) and cognitive ability scores (source data of Figure 1A in M&TC).

In this case, the strongest association between simulated thickness and cognition in the full sample ($n = 3,928$) is $r = -0.1129$. For this correlation, 80% power is reached at $n = 1,197$ after controlling for multiple comparisons ($q < 0.05$; Figure 1D, solid black line). Also, with a sample size of $n = 1,197$, the percentage of inflation is 7%, there is a 0% probability of observing opposite sign correlations for both unthresholded, and FDR corrected data, and the replication rate is 95%. In line with the previous simulation, other ROIs reach 80% power with $n \leq 2,000$ ($q < 0.05$; Figure 1D, solid grey lines). Instead, the average statistical power computed across ROIs is 11% at $n = 1,197$ ($q < 0.05$; Figure 1D, dotted line). For the same sample size, the average inflation is 90%, there is a 2% probability of observing opposite sign correlations across ROIs, and the average replication rate is 6%. As expected, smaller effect sizes ($|r| \approx 0.11$ as compared with $|r| \approx 0.16$) require larger samples ($n \approx 1,200$ as compared to $n \approx 600$) to be detected.

However, region-specific estimates of power, replication rate, and statistical errors show that small effect sizes ($0.11 < |r| < 0.16$) can be reliably detected with hundreds, not thousands, of participants.

To further prove that our findings do not depend on the synthetic nature of simulated correlations, we use HCP data ($n = 1,104$) and test the relationship between Freesurfer⁶ estimates of cortical thickness for 68 ROIs⁷ and a measure of fluid intelligence (PMAT24_A_CR; *hcp_parent_script.m*). Of note, among the numerous behavioral measures provided by the HCP consortium, we select this measure of fluid intelligence as there is at least one brain-behavior correlation in the full sample ($r = 0.1444$; Figure 1E) comparable to the largest reported in M&TC. In line with simulation results, the strongest relationship in HCP data reaches 80% power at $n = 639$ after controlling for multiple comparisons ($q < 0.05$; Figure 1E, solid black line). Using the same sample size and statistical threshold, we observe a 7% inflation rate and a 0% occurrence of opposite sign unthresholded and FDR-corrected correlations. Instead, at $n = 639$, the average statistical power is 39%, the average inflation rate is 28%, and there is a 0% probability of observing opposite sign results across ROIs. As far as replication rate is concerned, the strongest correlation has $> 90\%$ reproducibility with $n \cong 500$ (i.e., approximately half of the full HCP sample). In contrast, the average replication rate is 61% for the same sample size.

Hence, in line with simulations' findings, real data results indicate that small effect sizes can be detected reliably with hundreds of observations. Of note, estimates of statistical power obtained with the bootstrapping procedure in HCP data align with those computed using parametric statistics. Setting $r = 0.1444$ and $\alpha = 0.05$ (uncorrected), 80% power is achieved at $n = 352$ according to bootstrapping calculations and at $n = 374$ using a parametric method⁸.

In summary, our results indicate that (1) average estimates of power, replication rate, and statistical errors are biased and should not be used to draw inferences on the reproducibility of regional brain-behavior associations; (2) when applying a rigorous correction for multiple comparisons the probability of detecting and, thus, publishing opposite sign associations is null, even when sample sizes are extremely small (tens of individuals; Figure 1C-E opposite sign plot insert); (3) therefore, results obtained in fairly conducted small BWAS (e.g., no p-hacking, correction for multiple comparisons - all variables that affect the study reliability irrespectively of sample size) are more likely to be true and inflated, than false positives (with FWE $\alpha = 0.05$, only five studies out of 100 are expected to be false by chance).

That average estimates of power, replication rate, and statistical errors are unreliable is also evident when comparing ABCD results with those obtained from the UK Biobank (Figure 3 and Supplementary Figure 9, in the M&TC article). As pointed out by the authors, correlations obtained from the two datasets are comparable in terms of magnitude (Figure 2 in the original M&TC article); however, despite being almost eight times larger than the ABCD dataset, the

maximum average power achieved in the UK Biobank is ~75% at $n \cong 30,000$. This is a ~10% power increment (maximum average power in ABCD is 68%) following an eight-fold increase in sample size (full sample in ABCD is $n \cong 4,000$). This marginal increase hardly fits the steepness of average power reported in Figure 3 of M&TC (especially concerning the trajectory of the Bonferroni corrected estimate). Also, with a sample size of $n \cong 3,000$, the estimated average power in the UK Biobank is ~25% for the uncorrected threshold and ~0% for the Bonferroni corrected one (Supplementary Figure 9 of the original article). These estimates are substantially lower than those documented in the ABCD sample (i.e., ~65% at $n \cong 3,000$). One possible explanation for this discrepancy is that any non-zero correlation becomes significant with a large enough full sample size. Thus, the number of reference regions (i.e., those for which power, replication rate, and statistical errors are computed) increases with the number of observations in the full sample, and the presence of several small - yet significant - effects decreases the estimate of the average power at smaller sample sizes. To corroborate this claim, we simulate a distribution of brain-behavior correlations at three full sample sizes: $n = 4,000$, $n = 16,000$, and $n = 256,000$. Despite the distribution of correlation values being the same across the three full sample sizes, the M&TC estimate of average power decreases as the full sample increases (Figure 2A; *power_decrease_parent_script.m*). Paradoxically, at $n = 3,000$, average power ($q < 0.05$) drops from ~79% to ~33% with a 64-fold increase (from $n = 4,000$ to $n = 256,000$) of the full sample size. Importantly, single ROI estimates of power (as well as other metrics) do not depend on the size of the full sample. A single simulated correlation value of $r = 0.5300$ can be detected with 80% power at $n \cong 100$ ($q < 0.05$), regardless of the size of the full sample (Figure 2A). This further evidence indicates that average power estimates are inadequate to assess the reproducibility of effects distributed on the cortical mantle.

A possible counterargument to our criticism is that we selectively report results for the largest effect size and that a complex cognitive trait is unlikely to relate to the properties of a single brain region. Firstly, we have shown that multiple brain-behavior correlations yield adequate power with a sample size smaller than one thousand (Figure 1C-E). Moreover, researchers use magnetic resonance imaging to map functional specificity in the brain, and brain-behavior correlation studies are no exception. Searching for associations between phenotype and brain activity or structure, we expect a relationship to be expressed in some areas but not others. Therefore, in establishing general BWAS guidelines, it is essential to acknowledge brain functional specificity and emphasize that some effects can be replicated reliably with a relatively small sample size (i.e., a few hundred observations). Alternatively, researchers (as well as reviewers and editors) would be induced to believe that no effect has sufficient power to replicate, even when the sample size is 30,000 (as documented in Supplementary Figure 9 of M&TC). Also, it could be argued that researchers should aim at recruiting the largest possible sample for their studies. Although it may seem controversial to disagree with such a suggestion, we would like to emphasize that one of the reasons for conducting power calculations is to establish when to stop collecting data. Knowing when to stop data collection is of particular

importance as (1) even negligible effects with limited practical applications reach the statistical significance in very large cohorts⁹, and (2) it helps to optimize the balance between study value (i.e., relevance for the society) and participants' burden (e.g., scanning costs, participants' time, and effort)¹⁰.

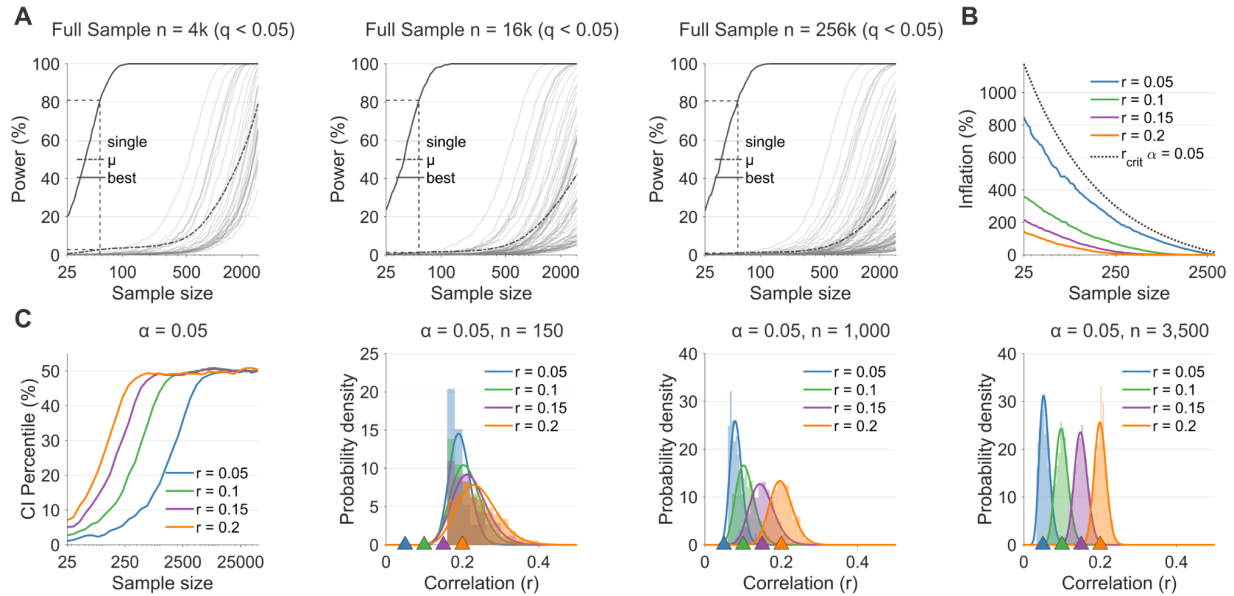


Figure 2. In **A**, we show that power estimates for the average method depend on the size of the full sample ($n = 4,000$ in the left panel, $n = 16,000$ in the central panel, and $n = 256,000$ in the right panel). Because any non-zero correlation becomes significant with a large enough full sample size, the number of reference regions (solid gray lines) increases with the number of observations in the full sample. The presence of several small - yet significant - effects (please compare the bottom right part of the three panels) decreases the average power estimate (dotted line) at smaller sample sizes. Instead, region-specific power estimates (dark solid line) do not depend on the size of the full sample. Panel **B** shows that effect size inflation results from statistical thresholding (dotted line). However, because larger population effects ($r = 0.20$, solid orange line) are more easily detected and less inflated in smaller samples, typically sized BWAS are more likely to report less inflated estimates of relatively larger true effects (as measured in the population) than extremely inflated estimates of relatively smaller population effects (e.g., $r = 0.05$ solid blue line). In **C**, we show that - because of statistical thresholding - effect sizes reported in the literature (i.e., the mean of the confidence interval) align with true effects measured in the population only when the sample size is large enough ($n \geq 606$ for $r = 0.20$, solid orange line; $n \geq 989$ for $r = 0.15$, solid purple line; $n \geq 2,064$ for $r = 0.10$, solid green line; $n \geq 8,986$ for $r = 0.05$, solid blue line). Not accounting for this effect determines overly optimistic estimates of the sample size required for replication. At larger sample sizes (third and fourth panels from the left), the effect of statistical thresholding diminishes, and effects reported in smaller studies ($n = 1,000$, $n = 3,500$) align with the population (colored triangles; population size $n = 100,000$ in the current simulation).

An important point raised by M&TC is that, in small sample studies, effect size inflation is the consequence of statistical thresholding and is aggravated by the pressure to publish positive findings. We document such an association by estimating the theoretical inflation percentage for correlation values corresponding to the critical $\alpha = 0.05$ at multiple sample sizes (Figure 2B; dotted line; *inflation_effect_parent_script.m*). In the original article, the authors refer to this issue

as the BWAS paradox. They suggest that the most inflated effects are most likely to be statistically significant at smaller sample sizes (pg. 657-8). However, by simulating the trajectory of inflation for four distinct effect sizes ($r = 0.05$, $r = 0.10$, $r = 0.15$, and $r = 0.20$; $n = 4,000$; $p < 0.05$ uncorrected), we show that the larger the effect size in the full sample, the smaller the inflation in studies with fewer participants (Figure 2B; e.g., orange vs blue curves). Importantly, larger effects (as measured in the full sample) are less inflated as well as more likely to pass the statistical significance threshold at smaller sample sizes. To demonstrate this, we use the M&TC resampling method and simulate 1,000 studies (sample size: $n = 200$) for each of the abovementioned correlations (4,000 studies in total). Results show that 1,410 out of 4,000 studies pass the significance threshold after correcting for multiple comparisons ($q < 0.05$). Of these 1,410 significant studies, the 49.79% are obtained from bootstrapping the full sample with a brain-behavior correlation of $r = 0.20$, whereas the 5.39% by resampling the one with a correlation of $r = 0.05$ (for completeness: the 29.57% comes from $r = 0.15$ and the 15.25% from $r = 0.10$). Therefore, typically sized BWAS are more likely to report less inflated estimates of relatively larger true effects (as measured in the population) than extremely inflated estimates of relatively smaller correlations observed in the population.

If typically sized BWAS can reliably detect small effects ($0.10 < |r| < 0.20$), why do we have replication failures? Leaving aside factors that affect study reliability regardless of sample size, such as malpractices (e.g., p-hacking, file-drawer issue), the inflation documented in smaller samples, and the lack of consideration for the confidence interval of the effect size may play a crucial role. Let's assume our goal is to replicate a BWAS reporting a correlation of $r = 0.30$ measured in 150 individuals ($\text{FWEp} < 0.05$; 95CI: 0.12 - 0.48). Firstly, since the authors have applied a rigorous correction for multiple comparisons and there is no reason to suspect misconduct, we should trust this finding. As mentioned above, correction for multiple comparisons ensures that the published study is more likely to report a true (inflated) effect than a false positive association. Because the aim is to replicate the effect for one significant region, we set $\alpha = 0.05$ and estimate that 85 individuals are required to detect an effect of $r = 0.30$ with 80% power. However, due to the relatively small sample included in the original study ($n = 150$), $r = 0.30$ is likely to be an inflated estimate of the true effect size in the population. Also, it should be pointed out that the range of estimates for the unknown parameter (i.e., the confidence interval) goes from $r = 0.12$ to $r = 0.48$. On these premises, estimating the replication sample size based on the reported effect (i.e., the mean of the confidence interval) is an overly optimistic choice. To demonstrate this and explore if and when the mean of the confidence interval (i.e., the effect size typically reported in published articles) should be trusted for power calculation, we simulate four effects ($r = 0.05$, $r = 0.10$, $r = 0.15$, and $r = 0.20$) in a full sample of 100,000 individuals (*sample_adjustment_parent_script.m*). For each effect, we create random resamplings at multiple sample sizes (as prescribed in M&TC), identify significant correlations at $p < 0.05$, and calculate the percentile of the confidence interval that best approximates the true effect (as measured in 100,000 individuals). In case of no inflation, the effect measured in the

full sample corresponds to the 50th percentile of the confidence interval of the effect reported in smaller studies. We show that the mean of the confidence interval is a proper estimate of the true effect $r = 0.20$ when the study sample is $n \geq 606$ (Figure 2C, first panel). Smaller effects require even more observations before the mean of the confidence interval aligns with the effect size measured in the full sample (Figure 2C, first panel): $n \geq 989$ for $r = 0.15$, $n \geq 2,064$ for $r = 0.10$, and $n \geq 8,986$ for $r = 0.05$. As expected, when the correction for multiple comparisons is applied (e.g., 100 ROIs, $p < 0.0005$), the alignment of the population effect with the mean of the confidence interval requires even larger samples: $n \geq 989$ for $r = 0.20$, and $n \geq 14,670$ for $r = 0.05$ (data not shown).

Thus, in case we aim to replicate a brain-behavior correlation estimated on a relatively small sample (e.g., 150 individuals), power calculation should not be based on the effect size reported in the original article. When power is computed assuming no inflation and ignoring the confidence interval of the effect, one cannot exclude that replication failures are due to optimistic estimates of the required sample size.

Unfortunately, the size of the effect in the population is unknown; therefore, it is difficult to predict how inflated an effect of $r = 0.30$ measured in 150 individuals precisely is. Nonetheless, considering the probability density function of significant correlations at $n = 150$ and $\alpha = 0.05$, it is implausible that such a correlation reflects an effect in the population of $r = 0.05$ (Figure 2C, second panel). Yet, it would be problematic to conclude whether a power calculation should be conducted considering $r = 0.20$ rather than $r = 0.15$. We cannot even rule out completely the possibility of a 200% inflation of the population effect $r = 0.10$. As expected, uncertainty decreases with increasing sample size (Figure 2C, third and fourth panels).

Hence, for the effect reported in the original article of our example ($r = 0.30$, $n = 150$), a more cautious power calculation based on the estimated population effect of $r = 0.15$ (target power 80%, $\alpha = 0.05$) prescribes the recruitment of 347 individuals, rather than 85 (see above).

The pressure to publish significant results is the main responsible for the effect size inflation present in the BWAS literature. For instance, although the sampling variability in smaller BWAS is high (Figure 1B, right panel), when no statistical threshold is applied, the average effect across studies (Figure 1B, right panel; solid dark line) represents an adequate estimator of the population effect, even when $n = 25$.

In conclusion, reproducible brain-behavior correlations do not necessarily require thousands of individuals. Average estimates of power, replication rate, and statistical errors are biased and should not be used to assess BWAS reproducibility. Indeed, fairly conducted small BWAS can detect small effects reliably and are unlikely to report false-positive results or opposite sign associations. Leaving malpractice aside, rather than the sample size per se, what biases the literature and exacerbates the replication crisis is the higher probability of publishing significant results. Publication bias determines the inflation of effect sizes, which is seldom considered when estimating the replication sample size.

Very large datasets are certainly needed to advance our knowledge of the association between brain and behavior. However, this should not translate into a hegemony of large consortia. We are convinced that studies on smaller samples are as important as those on large datasets. Typically sized BWAS carried out in individual laboratories increase sample diversity and representativeness in the published literature and promote the discovery of novel behavioral measures that, perhaps, relate more strongly to brain features¹¹.

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