

ANNEXES

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Title page

Is loss aversion a domain-general bias? On its extendibility in the food domain

Short title: Loss aversion in the food domain

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Abstract

Loss aversion is a cognitive bias influencing decision making, according to which potential losses have a larger psychological impact than potential gains of equal magnitude. Even if this bias has been extensively studied in the monetary domain, recent work has challenged its very existence, especially in the context of small symmetric stakes. Moreover, it is still unclear whether loss aversion is at play in other incentive domains. In this study, we empirically assessed monetary loss aversion for small symmetric stakes, as well as the extendibility of this bias to another domain, namely the food domain. We recruited a group of 58 female participants, who played two comparable gambling tasks in which they had to accept or reject mixed gambles involving either monetary or food outcomes. Through computational modelling we estimated loss aversion parameters in both the monetary and the food tasks. We found that participants showed loss aversion both in the monetary and in the food domain. Importantly, loss aversion in the monetary and food domain was positively correlated across participants (Spearman's $\rho = 0.48$, [95%CI 0.21 – 0.70], $p < 0.001$). Together, these results provide support for the existence of loss aversion even in the context of small symmetric monetary stakes, and further show that this bias seems to extend to at least the food domain, suggesting that it may be considered as a domain-general bias.

Keywords: loss aversion, prospect theory, decision-making, food

Introduction

A large body of research has shown that people often do not act as mere expected value maximizers when facing risky choices. For instance, in a heads or tails game, most people would reject a 50/50 chance to win 120€ or lose 100€, while the expected value (i.e., average net value over repeated trials) is positive. In order to account for such behavior, prospect theory has postulated that human behavior is influenced by a number of cognitive biases [1]. Among these biases is *loss aversion*, which describes the fact that losses tend to have a larger psychological impact than gains of equal magnitude [2–4]. As a consequence, the idea of losing a sum of money is experienced as more painful than the anticipated pleasure of earning the same amount, leading to decisions such as the rejection of the above gamble. While the concept of loss aversion was formulated in the monetary domain in the initial version of prospect theory [1], later developments emphasized its relevance in other domains such as trading goods [5] or job choices [6].

However, the pervasiveness of loss aversion bias has recently been questioned, sparking a debate as to whether loss aversion is indeed a universal and generalizable principle in line with a domain-general view as proposed by Kahneman and Tversky, or whether it is a more domain-specific bias likely to appear only under specific conditions. For instance, several moderators have been shown to influence loss aversion, such as age, level of education, and lack of knowledge or experience about the domain [2]. Additionally, substance use appear to impact loss aversion, as evidenced by studies indicating reduced or absent loss aversion bias in individuals with alcohol dependence, cocaine users, or current cigarette smokers [7–9]. Kahneman himself made an attempt to define the boundaries of loss aversion, emphasizing specific circumstances that are not subject to this bias, such as the context of an intentional trade [10]. Studies in the field of evolutionary psychology have also argued that loss aversion is highly sensitive to context and is influenced by underlying evolutionary-rooted motives [11,12]. Moreover, in recent debate, some authors have questioned the very existence of loss aversion, claiming that whether losses loom larger, equal to or smaller than gains is entirely dependent on the situation [13,14]. For instance, it has been argued that loss aversion disappears when making decisions based on experience [15–17]. In experimental economics some studies have shown that loss aversion only arises when the monetary stakes are high

enough [17–21], while the magnitude of the stakes also seems to influence temporal loss aversion [22]. Finally, it has been shown that loss aversion varies with the relative range of gains and losses involved; it appears to emerge primarily in situations with a narrow range of potential losses and a wide range of potential gains, rather than in scenarios with symmetric ranges of gains and losses [21,23]. Additionally, the rank position of gains and losses has been shown to influence the manifestation of loss aversion [24].

Although loss aversion is likely influenced by moderators [2], a body of previous work suggest that it may be a domain-general bias, viewing it as a fundamental and deeply-rooted behavior that has been preserved along evolution [25]. Of note, loss aversion has been acknowledged as an influential behavioral phenomenon in several decision-making theories, even before the advent of prospect theory [26]. It has often been conceptualized as an expression of an even more general bias -the negativity bias- according to which negative events overall have more psychological weight compared with positive ones [27]. In line with this domain-general conceptualization, loss aversion -which was originally formulated in the context of risky choice- has been extended to riskless choices [10]. As such, it has been proposed to play a role in a variety of empirical phenomena ranging from finance and marketing to psychology and political science, such as the endowment effect [2,5,28], the status quo bias [29], the sunk cost fallacy [30], the equity premium puzzle [31], and the enhanced sensitivity to disadvantages compared with advantages [4]. Nevertheless, whether these phenomena are truly driven by loss aversion is still widely debated, and various alternative accounts have been proposed over the years [14,32,33]. A handful of studies have also investigated whether loss aversion behavior is observed outside the monetary domain, testing its generalizability. While some studies have failed to provide evidence supporting this generalizability (such as in effort-based decision-making, where the asymmetry in the sensitivity to increasing vs decreasing effort fails to be captured by loss aversion [32], or in the context of social and environmental outcomes [35]), others have found supporting evidence. For instance, in marketing research on brand choice involving multiple properties such as price and quality, it has been shown that not only are people loss averse for both price and quality (i.e., more sensitive to losses than gains in price/quality) [36], but that loss aversion for quality is even stronger than loss aversion for price [37]. Loss aversion has also been observed for time [38] and in the health domain, with people showing loss aversion towards remaining

years of life [39,40]. In addition to laboratory studies, field work has also supported the role of loss aversion in everyday life, explaining for instance performance behaviors of professional golfers, soccer players, and football player [41–44], as well as the decision-making tendencies of sellers in the housing market [45].

The dearth of studies on loss aversion outside the monetary domain can be partly explained by the difficulty to quantitatively assess the relative value of positive and negative non-monetary prospects [27,46]. While it is straightforward to compare monetary prospects such as +100€ or -50€, it is far more difficult to similarly quantify gains and losses in domains such as quality or health. Some previous studies have effectively quantified non-monetary prospects, as in Strickland et al. [9], where gains and losses were measured in terms of cocaine quantities. Yet, most studies circumvent this issue by translating the value of non-monetary items onto a monetary scale -e.g., using willingness-to-pay procedures [12,36,39]- thus conflating monetary and non-monetary loss aversion. Alternatively, some studies resort to qualitative or observational (rather than quantitative or experimental) approaches, which are intrinsically limited for precisely measuring loss aversion [47]. Surprisingly, even within the monetary domain, only few studies allow for parametric quantitative estimation of loss aversion [47]. Finally, another issue in non-monetary domains is that it can be non-trivial to determine the location of a reference point in relation to which gains and losses are defined [39].

Overall, results of previous research illustrate the ongoing debate concerning the generalizability of loss aversion to different contexts, such as small and symmetric stakes or other incentive domains than the monetary one. In this study we aimed to address the above debate and tackle the question of loss aversion generalizability. We tested its extendibility to small symmetric monetary stakes, as well as to an independent domain, namely food. We chose the food domain because food is easily quantifiable (e.g., in terms of weight, volume, calories) and, as a natural reinforcer, is well suited to test the idea that loss aversion is deeply rooted and fundamental bias. We used a well-established “mixed gamble” task, in which participants have to accept or reject gambles offering a 50/50 chance of variable symmetric gains or losses. We employed a monetary version of this task [48], as well as a minimally-adapted version using juice gains and losses. We reasoned that, if loss aversion is indeed a

general bias, its influence should manifest even in contexts involving small and symmetric stakes and extend beyond monetary scenarios such as food.

Materials and Methods

Participants

The data were acquired between 14th March 2008 and 7th December 2009 in the context of a larger study (ENDANO cohort, ethical authorization of French *Comité de Protection des Personne*, n° 83-03 and 2688) that included various tasks and questionnaires in healthy volunteers as well as patients with anorexia nervosa (see Table S1 for an overview of the data collected). This study was conducted according to the principles of the Declaration of Helsinki. Participants were informed about the study and procedures, and they provided written informed consent before doing the experience. Note that one previous paper was published based partly on the same participants, but using entirely different data [49]. The present study focusses on the loss aversion task in healthy volunteers.

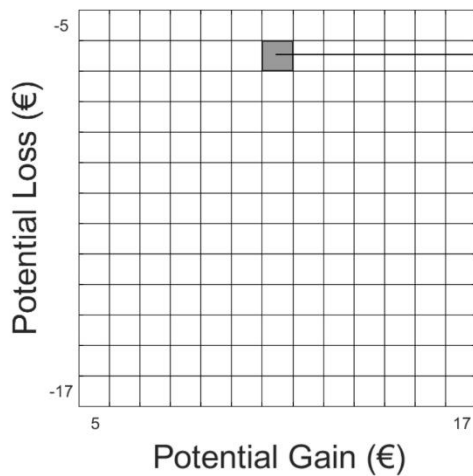
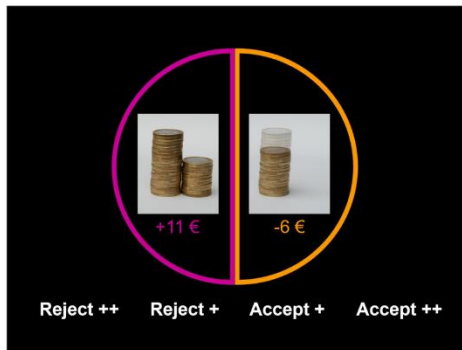
Sixty-seven healthy volunteers were recruited through advertisement. The following inclusion criteria were used: aged between 18 and 45 years old, female, fluent French speaker, no history of eating disorders, no psychological or neurological disorder, no current psychotropic medication, and normal or corrected-to-normal vision. We recruited only female participants because they also served as a matched control group for a group of patients with anorexia nervosa, a disorder that is much more prevalent in females than males [50]. A semi-structured psychiatric interview (Diagnostic Interview for Genetic Studies, DIGS, [51]) was performed by a trained psychologist (AV) with guidance from a senior psychiatrist (PG), and confirmed that none of the included participants suffered from lifetime psychiatric disorder.

Two participants were excluded for not completing the entirety of the two tasks. Additionally, seven participants were excluded from the analysis based on their extreme behavior (see “Participants exclusion” section). Therefore, the reported results are based on data from 58 healthy volunteers.

Experimental tasks

We used two versions of the same task, in the monetary domain and the food domain, both adapted from the loss aversion paradigm introduced by Tom et al. [48]. The two versions were designed to be as similar as possible. In both tasks, participants were asked to decide whether to accept or reject mixed gambles with a 50% chance of gaining a certain amount of money/juice, and a 50% chance of losing another amount of money/juice (Fig 1). They were instructed to make a decision within a 3-second timeframe (consistent with previous task design [48]), balancing the need for thoughtful consideration with task efficiency and participant engagement. We employed symmetric gambles (i.e., equivalent range of gains and losses), in which monetary gains and losses varied between 5 and 17€, in increments of 1€, while juice gains and losses varied between 3 and 15cl, in increments of 1cl (see gain-loss matrix in Fig 1). Thus, allow to investigate loss aversion within what can be considered as small stakes. Rather than using a rigid accept/reject decision rule [48], participants responded using a four-choice response scale that aligns more closely with real-life decision-making scenarios. This approach involves more nuanced considerations beyond binary choices and encourages participants to qualitatively reflect on the attractiveness of each gamble. Possible responses were “Accept ++” (strong willingness to accept), “Accept +” (moderate willingness to accept), “Reject +” (moderate willingness to reject) and “Reject ++” (strong willingness to reject). Choice was highlighted for 1s, and then a fixation cross appeared for 1s before a new gamble was presented. All possible gambling pairs from the gain-loss matrix (i.e., $13 \times 13 = 169$ trials) were presented to the participants in a random order. In case of no response within 3-seconds, a warning appeared, and the missed gamble was presented again later. Gains and losses were defined in relation to a reference point, which were visually depicted (see 1), corresponding to an initial endowment: in the monetary task, volunteers were endowed with a 20€ voucher, while in the food task, they were endowed an 18cl glass of juice. Participants were told that at the end of each task, one randomly chosen gamble would be played for real and that the outcome would be added or subtracted from the initial endowment (in case of a rejected gamble, the endowment would remain untouched). Both tasks started with a training part, at the end of which the random draw of one gamble was simulated in order to allow subjects to visualize the whole task’s procedure.

A. Monetary Task



B. Food Task

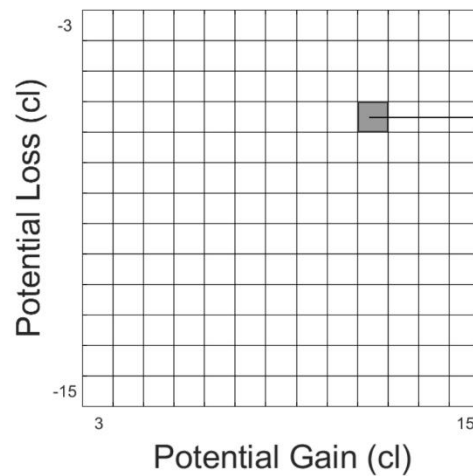
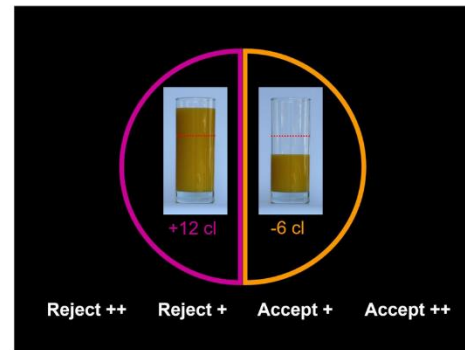


Fig 1. Task Design for the monetary task (A) and food task (B). For each task the 13x13 matrix represents all gambles presented to participants with 50/50 chance of gaining a certain amount of money or juice (x axis) or of losing a certain amount of money or juice (y axis). Participants had to answer to all the 169 possible gambles, which were randomly presented as shown here for one example for each task. Note that the reference point for gains and losses was visually salient: in the monetary task, it was materialized by the stack of 20 coins of 1€ on the left of the picture, while in the food task, it was materialized by the red dashed line indicating the 18cl endowment.

Both the monetary and the food tasks were administered in the same session, and their order was counterbalanced across participants. In order to maximize motivation for juice, participants could choose between three different types of juices (i.e., orange juice, tropical juice and apple juice), and were asked to fast (abstain from breakfast) in the 12 hours preceding the experiment, which always took place in the morning. Moreover, participant's

motivation to earn money and juice was measured using subjective ratings both before and after each task. Motivation was measured by means of a 5-point Likert scale, asking the participants to rate the pleasure they would expect from receiving the money or appetitive juice in that moment.

Participants received a compensation of 20€ in the form of a gift voucher for taking part in this study. As mentioned above, this amount could vary as a function of the outcome of the randomly chosen gamble played for real. The mean final compensation was 20.71€ (SD = 7, [min max] = [5€ 35€]). Similarly, the amount of earned juice also varied depending on the outcome of the random gamble played for real. The mean final volume was 19.00cl (SD = 5.97, [min max] = [6cl 33cl]).

Participants exclusion

A basic assumption of prospect theory is that participants are motivated to obtain rewards and thus behave as utility maximizers: they are more likely to accept gambles when potential gains increase and, conversely, less likely to accept gambles when potential losses increase. It is important to exclude participants whose behavior violates this basic assumption. To do this, we employed two strategies.

First, we used the subjective motivation ratings to identify participants with an extremely low motivation to earn money or juice (criterion #1). For each task and participant, we averaged the pre-task and post-task ratings, and excluded participants with an average score < 2 out of 5. Two participants were excluded based on this criterion for not being motivated to earn juice.

Second, we quantified the influence of gains and losses on participants' behavior using a logistic regression, similarly to previous studies [48,52]. Specifically, Accept or Reject decisions were modelled as a function of gain and loss magnitude, using the glmfit function in Matlab (version 2018a): $\text{Choice} = \beta_{\text{gain}} \times \text{Gain} + \beta_{\text{loss}} \times \text{Loss} + \text{Intercept}$. We excluded participants whose choices did not appear to be driven neither by gains nor losses, which was reflected by non-significance of both β_{gain} and β_{loss} (criterion #2, inspired from Botvinik-Nezer et al. [52]). Corresponding response matrices (see Fig S1 and S2) typically showed numerous violations of stochastic dominance, reflecting random behavior and/or a lack of understanding of the task.

This criterion also allowed us to identify participants with problematic convergence of parameter estimation, for instance due to small variance in their responses (i.e., too few accepted or rejected gambles). Four participants were excluded on this criterion in the monetary task and one participant was excluded in both tasks.

In total, 7 participants were thus excluded based on these criteria. Note that, for the sake of transparency, results of sensitivity analyses including these participants are reported in Table S2 and Fig S3.

Modelling

We used the framework of prospect theory to model participants' choice behavior, following the same approach as in our previous work [53]. Within that framework, the subjective utility of each gamble (SUG) can be approximated by the following equation:

$$\text{SUG} = p_{\text{Gain}} \times \text{Gain} - p_{\text{Loss}} \times \text{Loss} \times \lambda$$

In this equation, p_{Gain} is the gain probability and p_{Loss} is the loss probability. Given that both tasks employ mixed gambles with a 50/50 chance of gaining or losing a certain amount of money or juice, these probabilities are fixed, i.e., $p_{\text{Gain}} = p_{\text{Loss}} = 0.5$. *Gain* is the gain value of the gamble and *Loss* is the absolute loss value of the gamble. The relative weighting of gains and losses is reflected by the loss aversion parameter λ . A value of $\lambda > 1$ indicates overvaluation of losses relative to gains, reflecting a loss aversion bias, $\lambda < 1$ indicates overvaluation of gains relative to losses, while $\lambda = 1$ indicates equal valuation of gains and losses.

Participants' choices were reduced from a qualitative scale to a binary response, i.e., "Accept ++" and "Accept +" were pooled into an "Accept" category, while "Reject +" and "Reject ++" were pooled into a "Reject" category. The probability of accepting each gamble was then modelled with a softmax function, which was fitted to these binary choices:

$$P(\text{gamble acceptance}) = \frac{1}{1 + e^{-\mu (\text{SUG} + c)}}$$

This function includes two other parameters: a so-called "inverse temperature" parameter (μ) and a constant parameter (c). The constant parameter (c) reflects a value-independent gambling bias toward or away from gambling. If $c > 0$, there is a tendency to

accept gambles regardless of their subjective utility. If $c < 0$, there is a tendency to reject gambles regardless of their subjective utility (see Supplementary Methods and Results and Table S3 for more details about the rationale for including a constant parameter). The inverse temperature parameter reflects consistency of choice behavior. If $\mu = 0$, choices are random, whereas increasing values of μ reflect increasing consistency in choice behavior, with positive values of μ reflecting higher gamble acceptance with higher gain and lower loss value, and vice versa for negative values of μ .

Note that we made some simplifying assumptions in our modelling, similar to previous studies [2,48,53,54]. These simplifications limit the inflation of free parameters to be estimated, in order to maximize the reliability of this estimation. First, we assumed a linear valuation of gains and losses, in contrast to the curvilinear value function of prospect theory. This is a common and reasonable assumption [48,55,56], especially given the relatively narrow range of gains and losses used in our protocol, which make the curvature negligible. Additionally, the task employed was not optimized to reliably estimate this parameter [57]. Second, we assumed no subjective transformation of probabilities as described in prospect theory and assumed equal weights for the 0.5 probability of gains and losses. This is also a reasonable assumption given that the probability weighting function of prospect theory shows a shallow slope in the middle range of probabilities (i.e., around 0.5), reflecting low sensitivity to changes in probabilities in that range [58]. Also, it has been shown that individuals are less sensitive to probability differences in the context of mixed gambles [59].

Finally, it can be argued that since the reference point (corresponding to the initial endowments of 20€ and 18cl of juice) was visually salient in both tasks (see Fig 1), participants may have perceived gains and losses in the mixed gambles as increments and decrements from an initial gain. In other words, they may have interpreted the gambles as a 50/50 chance of a small gain (endowment - loss) vs a high gain (endowment + gain). Such a “gain framing” may have in turn decreased the attractiveness of the gambles not due to loss aversion, but due to risk aversion, i.e., the concave value function in the gain domain. In order to rule out this possibility, we performed additional model comparison analyses, in which we compared our loss aversion model to such a “risk aversion” model, aiming to determine which of these two models best describes participants’ behavior (see Supplementary Methods and Results).

Parameter estimation and statistical analyses

Parameter estimation was performed within the framework of Hierarchical Bayesian Inference (HBI), using the “computational and behavioral modeling” toolbox (<https://payampiray.github.io/cbm>) implemented in Matlab [60]. As a hierarchical approach, it has the advantage of regularizing participant-level parameters based on group statistics, therefore providing more reliable group-level parameters as well as better individual estimates. Moreover, as a fully Bayesian approach, HBI allows the assessment of uncertainty in parameter estimation by means of probability distributions [60], and has proven more accurate than non-hierarchical inference and hierarchical parameter estimation (i.e., showing a smaller estimation error). Importantly, HBI is also less sensitive to outliers, and thus more robust, compared with hierarchical parameter estimation methods [60].

First, we fitted our model to each participant’s data separately, in a non-hierarchical fashion, through Laplace approximation, employing gaussian priors (with mean 0, and variance 6.25 as suggested in Piray et al. [60]). This first step allows to define an approximation of posterior parameters at the individual level. Then, these estimated parameters were used to initialize the hierarchical Bayesian inference, which is an iterative algorithm. On each iteration, group mean and variance are updated based on individual parameters, serving as group mean and variance in the next iteration (known as empirical priors, since priors are constructed based on data). Iterations continue until the change in parameter values between two consequent iterations is considered small enough. Finally, group parameters are estimated using a weighted average, in which the influence of each participant on the group parameters depends on the extent to which the model is responsible for generating the dataset of that participant [60].

Since the estimated loss aversion parameters were not normally distributed, we employed non-parametric statistics using R (version 4.1.2). Specifically, we used a one-sample two-tailed Wilcoxon signed-ratio test (*stats* package) to assess whether mean loss aversion was significantly superior to 1 in both the monetary and food domains. Finally, we tested for a correlation between loss aversion in the monetary and the food domain, using Spearman’s rho coefficient (*stats* package) and Bayesian non-parametric correlation (*BayesFactor* package).

Results

Demographic characteristics

All included participants were females, with a mean age of 31.8 years (SD = 11.0) and a mean education level of 11.2 years (SD = 2.8) after level 2 of the International Standard Classification of Education (ISCED). The average monthly income of participants was 880€ (SD = 959).

Descriptive statistics

The mean subjective motivation ratings (measured by means of a 5-point Likert scale and averaged across the pre-task and post-task ratings) were respectively 4.22 (SD = 0.81) in the monetary domain and 3.68 (SD = 0.87) in the food domain.

Participants accepted on average 29% of the gambles (50/169 gambles; SD = 28) in the monetary domain and 37% (62/169 gambles; SD = 26) in the food domain. There was a positive correlation between the mean gamble acceptance in the food and the monetary domains (Spearman's $\rho = 0.56$, [95%CI 0.31 – 0.75], $p < 0.001$). Mean frequency of gamble acceptance across the gain-loss matrix is reported in Fig 2, while mean reaction times are reported in Fig S4.

Participants did not answer within the 3-second delay on 2.4% of the presented gambles on average, both in the food domain (4/169 gambles; SD = 6) and in the monetary domain (4/169 gambles; SD = 4).

Loss aversion in monetary and food domains

Model comparison analyses showed that participants' behavior was better explained by a loss aversion model than a risk aversion model (see Modelling section in Materials and Methods and Supplementary Methods and Results). We therefore reported group parameters for loss aversion, inverse temperature and the constant in Table 1. Mean subjective motivation ratings to earn money or juice were not correlated with group parameters, either in the monetary or food domain (see Supplementary Methods and Results).

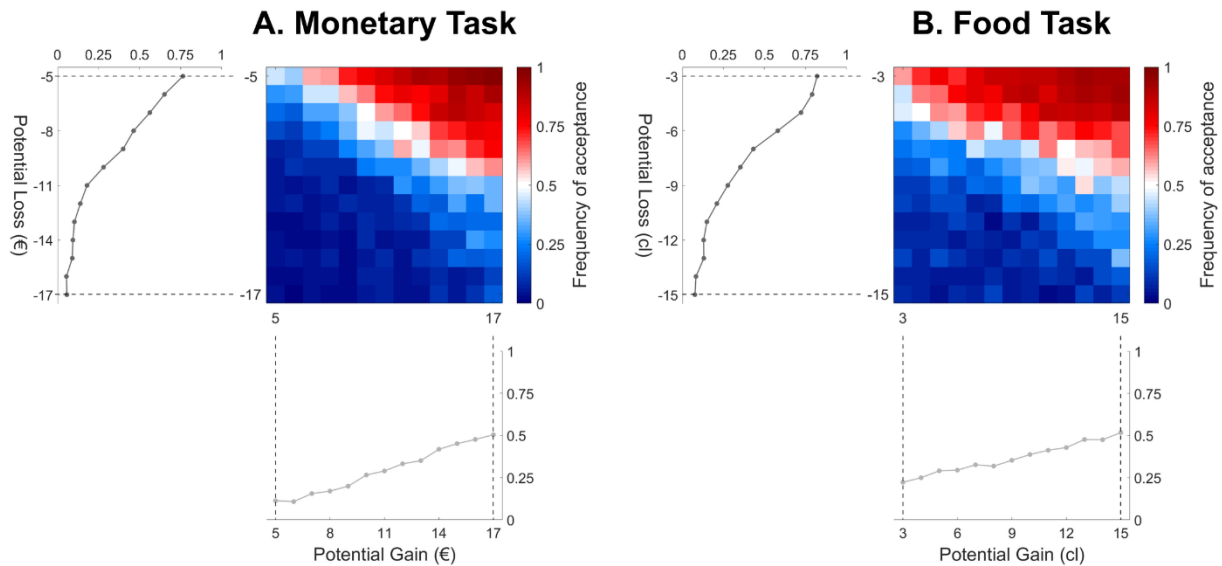


Fig 2. Frequency of gamble acceptance in the monetary task (A) and the food task (B). Heatmaps represent mean frequency of acceptance across participants as a function of gains and losses, with white color indicating a 0.5 frequency of acceptance, and red/blue colors indicating increasing frequency of acceptance/rejection of gambles. Note that, on average, participants are most uncertain in their responses (i.e., 0.5 frequency of acceptance) when gains are about twice as large as the losses, indicating loss aversion. The projection of frequency of acceptance along the gain axis (bottom) further depicts how acceptance unfolds with increasing gains, independently of losses (which are averaged). Similarly, the projection of frequency of acceptance along the loss axis (left) depicts how acceptance unfolds with increasing losses, independently of gains. Note that the slope for losses is steeper than the slope for gains, also reflecting loss aversion, i.e., faster change in frequency of acceptance for a similar change in losses compared with gains.

Table 1. Group parameters for the monetary and food loss aversion tasks ($n = 58$). Group means correspond to a weighted average output by the HBI procedure (see Parameter estimation and statistical analyses section in Materials and Methods). Note that since mean values have been argued to be biased towards loss aversion, median estimates are also reported, allowing for comparability with group metrics employed in previous studies [6,48].

	Monetary Task		Food Task	
	Group mean (standard error)	Group median (standard deviation)	Group mean (standard error)	Group median (standard deviation)
Loss aversion	1.87 (0.14)	1.78 (0.99)	2.81 (0.25)	2.86 (1.83)

Inverse temperature	1.01 (0.06)	0.99 (0.41)	0.76 (0.09)	0.61 (0.64)
Constant	1.74 (0.56)	1.31 (4.19)	5.22 (0.91)	3.59 (6.73)

According to the Wilcoxon signed-rank one-sample test, loss aversion parameters were significantly greater than 1 in the monetary task ($W = 1504$, [95%CI 1.53 – 2.15], $p < 0.001$) as well as in the food task ($W = 1535$, [95%CI 2.29 – 3.36], $p < 0.001$). Results of sensitivity analyses including all participants (i.e., no exclusions) also showed loss aversion parameters significantly greater than 1 (see Table S2).

Relationship between monetary and food loss aversion

Loss aversion values in the monetary and food domains showed a positive correlation across participants (Spearman’s $\rho = 0.48$, [95%CI 0.21 – 0.70], $p < 0.001$) (see Fig 3). Results of sensitivity analyses including all participants (i.e., no exclusions) also showed a significant positive correlation (see Fig S3).

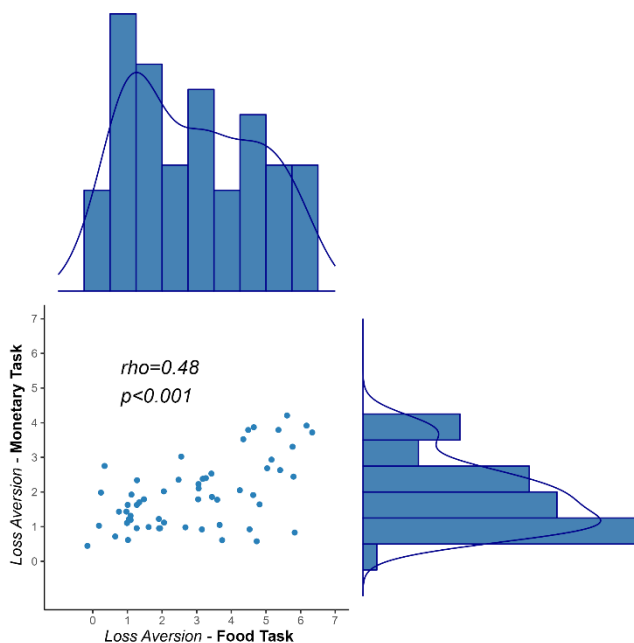


Fig 3. Correlation between loss aversion in the monetary and the food domains ($n = 58$). The histograms and density curves (top and right) show the distribution of loss aversion values in each domain.

The Bayesian correlation analysis yielded a $BF_{10} = 452$ (Kendall's tau = 0.35, [95%CI 0.16 – 0.50]), indicating that our data is 452 times more likely under the hypothesis of a positive relationship between monetary and food loss aversion (alternative hypothesis, H_1) than under the null hypothesis of no relationship between the two (H_0). Such a $BF_{10} > 10$ is usually considered as strong evidence for a positive relationship [50].

Discussion

In this study, we observed loss aversion behavior for small and symmetric monetary stakes, as well as for gambles involving gains and losses of fruit juice amounts, in a group of healthy female participants. These results provide some evidence for loss aversion extendibility beyond the monetary domain. Importantly, we also showed that monetary and food loss aversion were tightly correlated within participants. Overall, our results provide some evidence supporting the conceptualization of loss aversion as a domain-general individual trait.

First, we showed that loss aversion in the monetary domain was clearly observable even in the presence of low stakes and among female participants who were older than typical college student samples. This is an important observation in the context of previous critiques of loss aversion, which have suggested that loss averse behavior may have been overestimated due to the use of relatively high stakes among college students, who do not receive a regular income and may thus perceive monetary stakes as larger than older people [2]. Moreover, contrasting with previous critics [17,23,24,62] and consistent with some previous work [54–56], we could show that loss aversion was preserved when using symmetric distribution of gains and losses. Our mean estimate of monetary loss aversion is 1.87, i.e., well aligned with a recent meta-analysis reporting an average value of 1.96 [95%CI 1.82 – 2.1] [63].

Most importantly, our study shows that loss aversion is measurable in, and extendible to, the food domain. As such, participants perceived losses of juice as looming larger than corresponding gains of juice, corresponding to a loss behavior in the food domain. Moreover, loss aversion in the food domain was positively correlated with loss aversion in the monetary domain. Our study aligns with previous research, offering additional evidence against the alleged 'death' of loss aversion [2,64]. More generally, loss aversion behavior as observed in

both tasks is consistent with reaction patterns showing that participants tended to be most hesitant (i.e., longer reaction times) when deciding about gambles in which gains were about twice the losses (see Fig S4). However, this pattern was slightly less striking in the food domain, due to higher inter-individual variability in response times, probably more strongly influenced by contextual factors like thirst. Indeed, the level of thirst- measured by means of an open question on a 5-point Likert scale and averaged across the pre-task and post-task ratings- was correlated with reaction times in the food domain ($BF_{10} = 8.24$, Kendall's tau = 0.25, [95%CI 0.07 – 0.41]), while motivation for money was not correlated with reaction times in the monetary domain ($BF_{01} = 4.33$, Kendall's tau = -0.07, [95%CI -0.24 – 0.10]). It has been proposed that tendencies in decision-making under risk are deeply rooted in human evolutionary psychology, and represent an innate feature emerging early in human development. In line with this idea, loss averse behavior (partly via the endowment effect) has been observed in other primates such as capuchin monkeys and chimpanzees [25,65,66] (although see Farashahi et al. [67] who have reported steeper gain than loss curves in rhesus monkeys), as well as in non-primate animals such as pigeons [68,69]. In light of the probable evolutionary origins of this bias, it may thus not be surprising that loss aversion is also at play, or even greater, when considering survival-related reinforcement such as food, which has preceded more evolved and secondary rewards such as money. However, directly testing for differences between monetary and food domains poses challenges without establishing a clear correspondence between incentives (i.e., between 1€ and 1 cl of juice). Future research should try to establish this correspondence to enable meaningful comparisons of potential variations in loss aversion magnitude across different reward contexts.

Demonstrating the extension of loss aversion to the food domain among healthy individuals could hold significant clinical implications. For example, it prompts future research to explore whether the weight assigned to food losses vs gains is altered in eating disorders such as anorexia nervosa or binge eating disorder. This would build upon existing studies that have identified impairments in decision-making processes within these populations [49,70,71].

Of note, participants were on caloric restriction and thirsty when performing the experiment, as they had been asked to fast for the 12 preceding hours. Under these

conditions, one might argue that the desire to gain a prompt food reward could have been fueled by the urge to respond to a physiological need, contributing to maximizing loss aversion in the food domain. Yet, there was no correlation between the level of thirst and loss aversion (as well as between the level of thirst and constant and inverse temperature parameters) in the food domain (see Supplementary Methods and Results). This result thus suggests that food loss aversion was independent of physiological thirst level.

This study has several limitations. First, the sample size employed in this study was relatively small, although larger than most previous studies [48,72,73]. Future studies should try to replicate the present results in larger samples. Second, all participants were females, which prevents us from extending our results to the male population. In particular, it has been proposed that sex might impact loss aversion, and that females might show a stronger loss aversion bias [74,75]. Future studies should explore potential sex differences in the context of loss aversion in the food domain. Future research should also investigate whether loss aversion is extendible to other food categories than juice, as well as other domains than food. Third, as detailed in the Materials and Methods section, the use of an initial endowment serving as a reference point for gains and losses may have induced a “gain framing” context, in which the attitude towards gambles would have been driven by risk aversion (concave value function) rather than loss aversion. Although our model comparison procedure suggested this was unlikely (see Supplementary Methods and Results), future studies may want to replicate the current findings while using a zero reference point unambiguously framing the gambles’ options as gains and losses. Finally, it should be noted that the design of our mixed gamble task has been criticized for biasing participants towards loss aversion, given that the status quo is to reject the gamble option [18,21]. While we tried to mitigate this possibility by using a constant parameter in our modelling -aiming to capture such a value-independent bias- it is still possible that loss aversion values may have been slightly over-estimated in our study.

Despite these limitations, we believe that our study provides empirical evidence that loss aversion can be quantified and extended beyond the monetary domain. As such, our results provide some support for the conceptualization of loss aversion as a domain-general bias.

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Ethics approval: This study received the ethical authorization of the French *Comité de Protection des Personne* (n° 83-03 and 2688).

Consent to participate: Participants were informed about the study and procedures and signed an informed consent before doing the experience.

Consent for publication: Not applicable.

Authors' contribution: XC, JCD, PG, NR, GS, and AV designed and conceptualized the research. AV collected the data. AMF, SL and GS analyzed and interpreted the data. AMF and GS drafted the manuscript. All authors were involved in the critical revision of the manuscript and approved the final manuscript for submission.

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SUPPLEMENT

Are Brain Responses to Emotion a Reliable Endophenotype of Schizophrenia? An Image-based fMRI Meta-analysis

Fiorito *et al.*

Contents:

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Supplementary Methods

Study exclusion

27 studies were excluded due to the following reasons:

- 8 studies employed the same dataset as in another included study(1–8)
- 8 studies used non-relevant task design (1 non-visual stimuli(9), 1 non-visual stimuli and conditioning task(10), 1 positively valenced emotional stimuli(11), 1 Theory of Mind task(12,13), 1 stress induction task(14), 1 rejection-acceptance task(15), 1 Stroop task using words(16))
- 4 studies were conference abstracts(17–20)
- 3 studies did not perform group comparisons(21–23)
- 2 studies were systematic reviews or meta-analyses(24,25)
- 1 study was a methodological paper(26)
- 1 study provided dubious data(27). Reasons for questioning the reliability of this study were that within-group T-maps showed highly unexpected results in healthy controls, opposite to what is typically observed in studies of emotional processing; unfortunately, the authors declined to engage in double-checking their results when we invited them to, so we preferred to exclude this study

Criteria for contrast selection

When more than one article was published using the same sample of participants, we favored the article using methods most closely aligned with our inclusion criteria (e.g., we discarded studies that only report region of interest (ROI) results in favor of studies that report whole-brain analyses), and then we favored the one that could provide the contrast maximizing homogeneity between studies. When more than one contrast from the same study was available, we chose the contrast expected to maximize amygdala activation (e.g., contrasts related to the implicit rather than explicit condition(28), or, when a contrast with all negative emotions pooled together was not available, a contrast favoring fearful stimuli over other emotions(29)). Finally, in keeping with the goal of specifically isolating emotional processing regardless of content, when possible we preferred contrasts of the form negative emotional stimuli versus neutral stimuli, rather than negative emotional stimuli versus control condition/implicit baseline.

Partial brain coverage inclusion

There is a common consensus regarding the need to exclude studies only employing ROI analyses, in order to avoid biasing whole-brain results in favor of these regions(30). In this meta-analysis, ROI studies were thus excluded. However, we included one study that used a thick-slab acquisition -and thus had a partial brain coverage(31)- given that this coverage was much wider than classical ROIs and encompassed the main brain regions typically involved in emotion processing such as the amygdala (see Supplementary Figure S1 in Wolf et al., 2011 for an image of the thick-slab acquisition employed).

Also, it is important to note that, since the latest version of SDM (SDM-PSI 6.21) no longer assumes a uniform distribution of false positive foci and does not test for spatial convergence, inclusion of studies with partial brain coverage does not

necessarily lead to increased Type I errors. On the contrary, this could increase Type II errors in regions not covered by these studies(32).

Heterogeneity, publication bias and robustness

I^2 statistic, which represents the percentage of total variation due to between-study heterogeneity rather than sampling error, was visually inspected at the whole-brain level through the I^2 statistic heterogeneity map (a meta-analytical map storing for each voxel a value of I^2 statistic). Heterogeneity is considered to be low when I^2 values are below 40%, moderate when I^2 values are between 30-60%, substantial when I^2 values are between 50-90%, and considerable when I^2 values are between 75-100%(33). The inspection of the heterogeneity map suggests the presence of low or moderate heterogeneity almost across the whole brain, with only few clusters indicating substantial heterogeneity (see Figure S2). Moreover, I^2 statistic values were extracted from amygdala ROIs with SDM-PSI. The presence of low heterogeneity in the amygdala was suggested by low I^2 statistics in the left ($I^2=10.6\%$) and the right ($I^2=15.5\%$) amygdala. This was also reflected by all included studies lying inside the triangular region of the funnel plot (see Figure 3C in the main text).

Additional analyses were conducted to explore the possible importance of between-study heterogeneity on the results. In order to determine whether results differ according to the definition of “at risk of schizophrenia” (i.e., familial risk, clinical high risk, or psychometric risk), we performed three whole-brain subgroup meta-analyses. The effect of the type of contrast (i.e., negative emotional versus neutral stimuli contrast, or negative emotional versus control condition/implicit baseline contrast) as well as the effect of the task itself (i.e., implicit or explicit task) were also addressed through whole-brain subgroup meta-analyses. We also ran an additional analysis only including studies employing faces, in order to further homogenize the stimuli used across several tasks. Finally, a whole-brain meta-regression with a linear model using participants’ mean age as a regressor was performed to see whether age differences across studies influenced the results. Due to the limited number of studies included in subgroup analyses, and in order to reduce the increased risk of Type I error associated with multiple tests, results of additional analyses were thresholded at $p_{TFCE}<0.005$ as previously done in Dugré et al., 2020(34). No statistically significant results were found in either of the above sensitivity analyses.

Publication bias was assessed in amygdala ROIs, first through visual inspection of the funnel plot, which represents precision of each study as a function of its effect size. In the absence of publication bias, studies are expected to be symmetrically distributed (see Figure 3C in the main text for visual inspection of publication bias). Secondly, we used Egger’s regression test, a quantitative method that tests for the presence of asymmetry in the funnel plot, which was not significant for either left ($z=-0.02$, $p=0.98$) or right ($z=-0.65$, $p=0.52$) amygdala, indicating reasonable symmetry of the funnel plot and thus no evidence of a publication bias.

Finally, we performed sensitivity analyses for the purpose of examining the robustness of results and identifying outlier studies. For this analysis, we used a jackknife procedure, consisting of discarding one whole-brain T-map of the meta-analysis dataset at a time. The lack of significant differences in brain activation in at-risk individuals compared with healthy controls was replicated in all whole-brain jackknife analyses, suggesting that this lack of significance was not driven by single outlier studies.

Partial coverage of the amygdala

The proximity of the amygdala to the sphenoid sinus makes the BOLD signal in this region more vulnerable to susceptibility artifacts caused by air-tissue interface(35). The resulting dropout of the BOLD signal in this region led to partial coverage of the amygdala in several studies included in this meta-analysis(36–40). In order to limit the influence of this partial coverage at the group-level, the authors of these studies were contacted and asked to rerun their analyses after modifying an SPM default parameter (all studies used SPM). Indeed, in order to create first-level brain masks, SPM employs a default threshold that restricts the statistical analyses only to voxels that exhibit a value that is at least 80% of the mean global signal present in the data. If there is signal dropout in at least one participant, for instance due to susceptibility artifacts, the second-level mask (which corresponds to the intersection of first-level masks) will not cover this region. Therefore, authors were asked to rerun analysis after changing the default threshold parameter from 80% to 20%, in order to enlarge first-level brain masks, while also applying an explicit mask excluding voxels outside of the brain.

Two authors successfully engaged in this process and could provide T-maps with an improved coverage of the amygdala(36,40). Three studies with a partial amygdala coverage were still included since authors could not perform the requested analysis due to time restrictions(37–39).

Future studies, and particularly those targeting commonly artefacted regions like the amygdala, should employ acquisition protocols that counteract the negative consequences of these artifacts(41).

Supplementary Table S1. PRISMA Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Introduction
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Introduction
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Methods and Materials (<i>Inclusion of studies; Study characteristics</i>)
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Methods and Materials (<i>Inclusion of studies</i>)
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Methods and Materials (<i>Inclusion of studies</i>)
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Methods and Materials (<i>Inclusion of studies</i>); Supp Methods
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Methods and Materials (<i>Inclusion of studies</i>)
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Methods and Materials (<i>Inclusion of studies</i>); Supp Methods
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or	Methods and Materials (<i>Study characteristics</i>); Table 1; Table S2

Section and Topic	Item #	Checklist Item	Location where item is reported
		unclear information.	
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	NA
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Figure 3
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Methods and Materials (<i>Inclusion of studies</i>)
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	NA
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Methods and Materials (<i>ROI Analyses (frequentist and Bayesian)</i>)
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Methods and Materials; Supp Methods
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Supp Methods
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Supp Methods
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Supp Methods
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Methods and Materials (<i>Whole-brain Bayesian analyses</i>)
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Methods and Materials (<i>Inclusion of studies</i>); Figure S1

Section and Topic	Item #	Checklist item	Location where item is reported
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Supp Methods
Study characteristics	17	Cite each included study and present its characteristics.	Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	NA
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Figure 3
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Table 1; Table S2; Figure 3
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Results; Figure 3; Figure S2
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Results (<i>Heterogeneity, publication bias and robustness</i>); Supp Methods
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Results (<i>Heterogeneity, publication bias and robustness</i>); Supp Methods
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Figure 3, Supp Methods
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Results (<i>Whole-brain Bayesian analyses</i>)
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Discussion
	23b	Discuss any limitations of the evidence included in the review.	Discussion; Supp Methods
	23c	Discuss any limitations of the review processes used.	Discussion

Section and Topic	Item #	Checklist item	Location where item is reported
	23d	Discuss implications of the results for practice, policy, and future research.	Discussion
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Methods and Materials (<i>Inclusion of studies</i>)
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Methods and Materials (<i>Inclusion of studies</i>)
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Acknowledgment and disclosures
Competing interests	26	Declare any competing interests of review authors.	Acknowledgment and disclosures
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Results

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: <http://www.prisma-statement.org/>

Supplementary Table S2. Demographic and methodological characteristics of included studies

Source	Age, Mean (SD)	Male Sex, No. (%)	MRI Field strength
Bourque et al., 2017(42)	At risk: 14.26 (0.3); HC: 14.35 (0.4)	At risk: 10 (35.7); HC: 47 (34.8)	3T
Cao et al., 2016(43)	At risk: 33.29 (12.6); HC: 32.69 (10.1)	At risk: 20 (34.5); HC: 39 (41.5)	3T
de Achával et al., 2012(40)	At risk: 30.4 (4.8); HC: 28.4 (8.3)	At risk: 8 (57.1); HC: 8 (57.1)	3T
Diwadkar et al., 2012(36)	At risk: 14.3 (3.1); HC: 14.6 (2.6)	At risk: 12 (63.2); HC: 16 (66.7)	4T
Modinos et al., 2010(44)	At risk: 19.8 (1.8); HC: 21 (2.8)	At risk: 7 (41.2); HC: 7 (41.2)	3T
Modinos et al., 2015(37)	At risk: 24.4 (4.1); HC: 23.8 (4.6)	At risk: 10 (55.6); HC: 10 (45)	1.5T
Modinos et al., 2017(39)	At risk: 27.36 (7.6); HC: 27 (5.6)	At risk: 10 (47.6); HC: 13 (59.1)	3T
Park et al., 2016(45)	At risk: 23.9 (5.6); HC: 23.06 (3.9)	At risk: 7 (35); HC: 8 (47.1)	3T
Pulkkinen et al., 2015(46)	At risk: 22.4 (0.8); HC: 22.3 (0.7)	At risk: 20 (39.2); HC: 20 (38.5)	1.5T
Quarto et al., 2018(47)	At risk: 35.4 (10.1); HC: 31.4 (10.4)	At risk: 13 (36.1); HC: 30 (53.6)	3T
Rasetti et al., 2009(48)	At risk: 34.8(1.8); HC: 31.8 (2.2)	At risk: 16 (55.2); HC: 15 (75)	3T
Spilka et al., 2015(49)	At risk: 41.19 (15.5); HC: 40.7 (11.1)	At risk: 10 (37); HC: 13 (48)	3T
van der Velde et al., 2015(38)	At risk: 23.1 (4.4); HC: 22.1 (3.6)	At risk: 8 (53); HC: 8 (50)	3T
Shivakumar et al., in preparation(50)	At risk: 29 (1.7); HC: 31 (4.8)	At risk: 12 (92.3); HC: 11 (73.3)	3T
Wang et al., 2018(51)	At risk: 19.21 (0.9); HC: 19.23 (0.9)	At risk: 17 (50); HC: 13 (43.3)	3T
Wolf et al., 2011(31)	At risk: 42.3 (14.8); HC: 39 (10.7)	At risk: 9 (45); HC: 12 (48)	3T
Wolf et al., 2015(52)	At risk: 15.7 (2.7); HC: 16.6 (3.0)	At risk: 123 (47.3); HC: 104 (47.3)	3T

Abbreviations: HC, Healthy Controls

Supplementary Table S3. MNI coordinates of within-group frequentist meta-analysis We employed the Hammersmith brain atlas (n30r83, © Copyright Imperial College of Science, Technology and Medicine 2007. All rights reserved(53)) in order to determine the name of brain structures

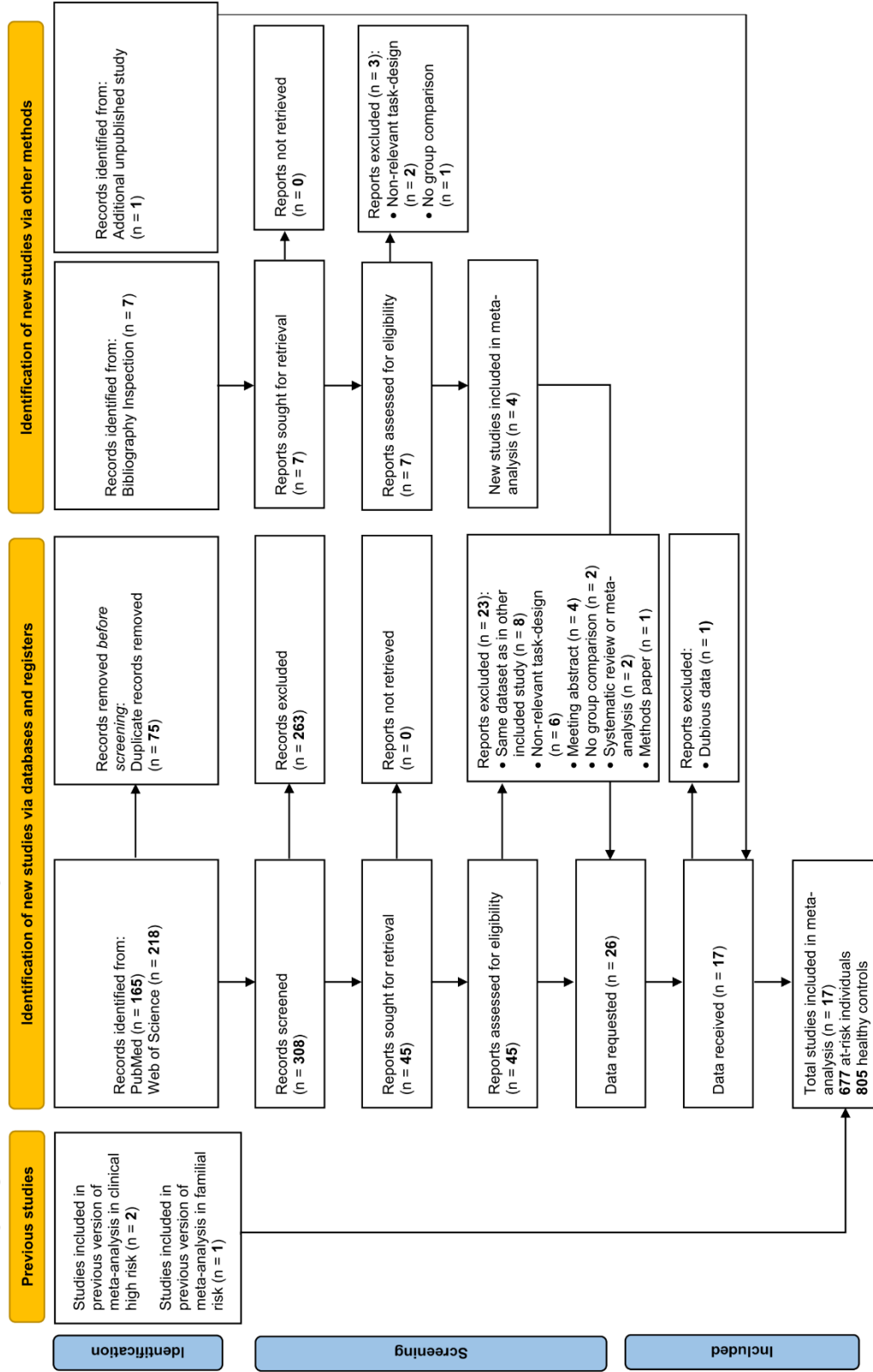
Brain region	Hemisphere	MNI (x,y,z)	SDM-Z
<i>Healthy controls - activations</i>			
Posterior/lateral orbital gyrus	Right	36,28,-8	4.323
Anterior medial temporal lobe	Right	38,6,-32	4.310
Inferior frontal gyrus	Right	48,30,16	4.076
Thalamus	Right	6,-6,4	4.043
Thalamus	Left	-4,-10,4	4.000
Posterior/lateral orbital gyrus	Left	-40,42,-10	4.394
Middle frontal gyrus	Left	-36,34,14	4.010
Inferior frontal gyrus	Left	-42,28,-8	3.879
Amygdala	Left	-22,-6,-18	3.698
Anterior part of superior temporal gyrus	Left	-44,16,-26	3.625
Cerebellum	Right	32,-80,-32	4.875
Posterior temporal lobe	Right	38,-62,-20	4.420
Lateral occipital lobe	Right	40,-72,-14	3.932
Cerebellum	Left	-36,-48,-34	4.431
Lateral occipital lobe	Left	-32,-80,-14	4.325
Temporal horn of lateral ventricle	Left	-30,-22,-10	2.800

Brain region	Hemisphere	MNI (x,y,z)	SDM-Z
Amygdala	Right	22,-4,-18	3.299
<i>Healthy controls - deactivations</i>			
Postcentral gyrus	Right	50,-14,16	-5.161
Insula	Right	44,-6,4	-5.057
Posterior superior temporal gyrus	Right	64,-12,6	-5.043
Inferiolateral parietal lobe	Right	50,-24,22	-3.832
Posterior superior temporal gyrus	Left	-62,-24,8	-5.859
Postcentral gyrus	Left	-54,-16,14	-5.647
Inferiolateral parietal lobe	Left	-44,-26,22	-4.821
Insula	Left	-38,-20,6	-3.826
Precentral gyrus	Right	8,-24,52	-4.053
<i>At risk - activations</i>			
Cerebellum	Left	-28,-78,-32	5.776
Lateral occipital lobe	Left	-42,-68,-16	5.404
Lateral occipital lobe	Right	40,-66,-18	5.244
Cerebellum	Right	38,-56,-26	4.398
Thalamus	Right	4,-16,12	4.828
Thalamus	Left	-14,-16,18	4.599
Caudate nucleus	Right	12,6,8	4.496

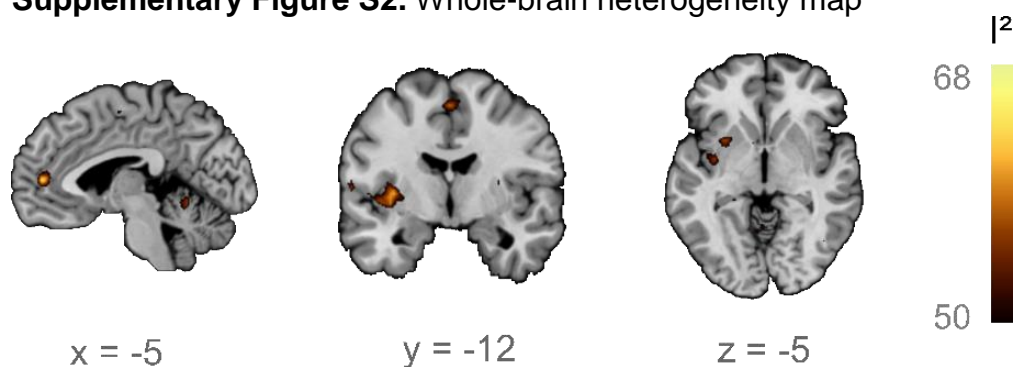
Brain region	Hemisphere	MNI (x,y,z)	SDM-Z
Insula	Right	32,-6,-18	4.309
Posterior orbital gyrus	Left	-26,10,-16	4.147
Inferior frontal gyrus	Left	-48,36,-8	5.107
Middle frontal gyrus	Left	-48,46,8	5.021
Inferior frontal gyrus	Right	44,20,16	6.422
Anterior part of superior temporal gyrus	Right	52,18,-16	4.906
Middle frontal gyrus	Right	32,8,30	4.431
Superior frontal gyrus	Right	2,16,54	4.848
Superior frontal gyrus	Left	-6,32,50	4.704
Posterior temporal lobe	Right	52,-42,-2	3.713
Amygdala	Left	-28,0,-19	3.763
Amygdala	Right	26,0,-19	3.713
<i>At risk - deactivations</i>			
Postcentral gyrus	Right	62,-6,8	-5.317
Posterior superior temporal gyrus	Right	62,-6,4	-5.105
Middle inferior temporal gyrus	Right	62,-16,-22	-4.389
Pre-subgenual frontal cortex	Left	-10,32,-10	-5.094
Superior frontal gyrus	Right	4,46,-4	-4.482

$p_{TFCE} < 0.05$

Supplementary Figure S1. Flow Chart outlining the selection procedure of studies



Supplementary Figure S2. Whole-brain heterogeneity map



Heterogeneity map displaying for each voxel the I^2 statistic. Since an I^2 statistic above 50% is commonly interpreted as substantial heterogeneity, the map was thresholded at $I^2 > 50\%$. A few small clusters displayed evidence of substantial heterogeneity in bilateral superior frontal gyrus, cerebellum, posterior temporal lobe, substantia nigra and left insula. Functional T-maps are overlaid on the Colin 27 anatomical template.

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SUPPLEMENTARY MATERIAL

Blunted brain responses to neutral faces in healthy first-degree relatives of patients with schizophrenia: an image-based fMRI meta-analysis

Fiorito *et al.*

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Supplementary Figure S6. Whole-brain heterogeneity map

References

Supplementary Methods

Literature search

PubMed search employed a combination of the following keywords: (“schizophren*” OR “psychosis”) AND (“relatives” OR “first-degree” OR “siblings” OR “twins” OR “brothers” OR “sisters” OR “offspring” OR “parents” OR “genetic risk”) AND (“neuroimaging” OR “fMRI” OR “functional Magnetic Resonance Imaging”) AND (“emotion*” OR “affect” OR “mood” OR “face” OR “facial”).

Web of Science review was based on the following keywords: TS=(schizophren* OR psychosis) AND TS=(relatives OR first-degree OR siblings OR twins OR brothers OR sisters OR offspring OR parents OR genetic risk) AND TS=(neuroimaging OR fMRI OR functional magnetic resonance) AND TS=(emotion* OR affect* OR mood OR face OR facial).

Study exclusion

50 studies were excluded due to the following reasons:

- 12 studies did not include neutral faces¹⁻¹²
- 11 studies used non-relevant task design (1 structural magnetic resonance imaging¹³, 2 non-visual stimuli^{14,15}, 2 resting state^{16,17}, 6 studies employed scenes or stories instead of faces¹⁸⁻²³)
- 7 were conference abstracts²⁴⁻³⁰
- 7 studies employed the same dataset as in another included study³¹⁻³⁷
- 6 studies were systematic reviews or meta-analyses³⁸⁻⁴³
- 6 study did not include a group of first-degree relatives⁴⁴⁻⁴⁹
- 1 study was a method paper⁵⁰

*Sensitivity analysis combining **image- and coordinate-based meta-analysis***

In order to assess the robustness of our image-based meta-analytic results, we performed a sensitivity analysis wherein we added 2 studies reporting brain coordinates. The SDM methodology allows to conduct such meta-analyses that combines 3D statistical images and peak coordinates by leveraging its ability to reconstruct 3D statistical maps from image coordinates. This involves converting t-values of peak coordinates into effect sizes and gradually imputing effect sizes for surrounding voxels, considering proximity to peaks and accounting for estimation inaccuracies through multiple imputations^{51,52}.

Table S1. Quality assessment checklist adapted from Zheng et al., 2018⁵³. For each study and each item, a score of 0/0.5/1 is assigned (0 if criteria not met, 0.5 if partially met, 1 if clearly met). Total score is 12 out of 12.

Category 1: Sample characteristics

Patients were evaluated with specific standardized diagnostic criteria

Important demographic data (age, gender, and education) were reported with mean (or median) and standard deviations (or range))

Healthy comparison subjects were evaluated to exclude psychiatric and medical illnesses

Important clinical variables were reported with mean (or median) and standard deviations (or range))

Sample size per group > 10

Category 2: Methodology and reporting

Whole brain analysis was automated with no a-priori regional selection

Magnet strength at least 1.5T

Whole brain coverage of fMRI scans

The acquisition and preprocessing techniques were clearly described so that they could be reproduced

Coordinates reported in a standard space

Significant results are reported after correction for multiple testing using a standard statistical procedure (FDR, FWE or permutation-based methods)

Conclusions were consistent with the results obtained and the limitations were discussed

Table S2. Main objective and main results of the included studies

Reference	Main objective	Main results	Quality score
Diwadkar et al., 2012 ⁵⁴	To investigate effective brain connectivity associated with emotional processing in schizophrenia	Abnormal connectivity during emotion processing in offspring of patients with schizophrenia	11
Oertel et al., 2019 ⁵⁵	To investigate associative memory in schizophrenia	Abnormal brain activity during retrieval in patients with schizophrenia and to a lesser degree in first-degree relatives	12
Park et al., 2016 ⁵⁶	To investigate implicit emotion processing in schizophrenia	Abnormal brain activity to fearful and neutral faces in first-degree relatives	11
Pirnia et al., 2015 ⁵⁷	To investigate associative memory in schizophrenia	Abnormal brain activity to successful encoding in patients with schizophrenia	11.5
Quarto et al., 2018 ⁵⁸	To investigate effective brain connectivity associated with emotional processing in schizophrenia	Abnormal connectivity during emotion processing in both schizophrenia patients and first-degree relatives	11.5
Spilka et al., 2015 ⁵⁹	To investigate implicit emotion processing in schizophrenia	Abnormal brain activity to emotions in first-degree relatives and patients with schizophrenia.	11.5
Wolf et al., 2011 ⁶⁰	To identify and modulate emotion processing in schizophrenia	Abnormal brain activity to emotion identification induced by GABAergic modulation in first-degree relatives	11

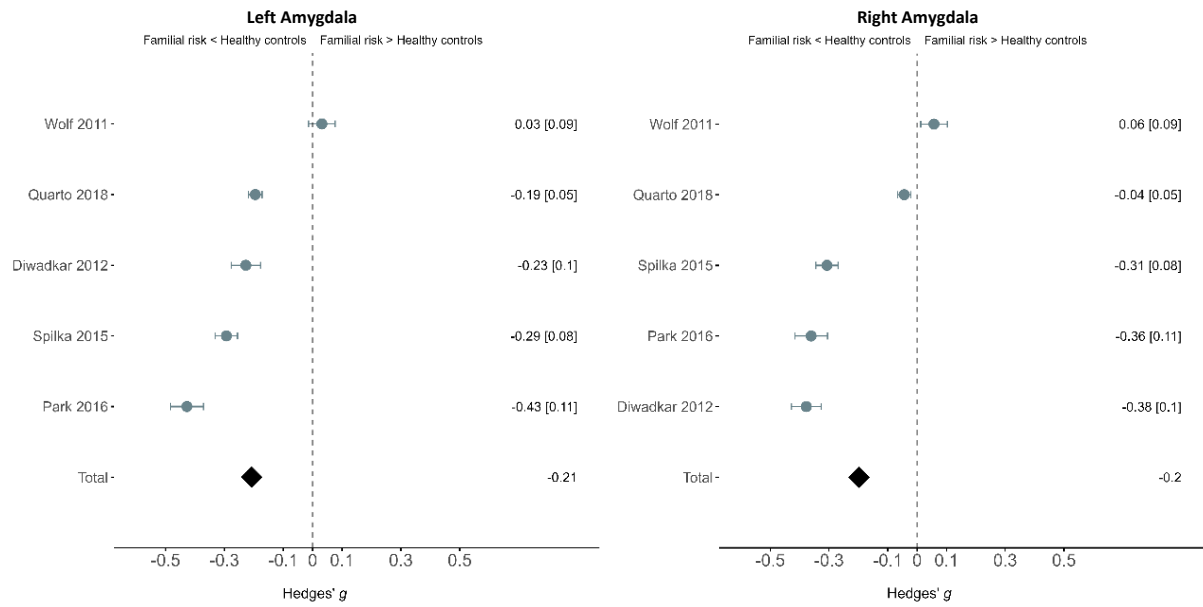
Table S3. MNI coordinates of within-group meta-analysis. We employed the Hammersmith brain atlas (n30r83, © Copyright Imperial College of Science, Technology and Medicine 2007. All rights reserved⁶¹) in order to determine the name of brain structures.

Brain region	Hemisphere	MNI (x,y,z)	SDM-Z
<i>Healthy controls - Activations</i>			
Amygdala	Left	-22, -3, -16	4.5863
Amygdala	Right	22, -3, -14	4.4872
Insula	Left	-32, 4, -10	5.2278
Insula	Right	32, 4, -4	4.8726
Putamen	Left	-22, 8, 6	5.4896
Putamen	Right	26, 7, -2	5.7281
Occipital lobe (Fusiform Face Area)	Left	-44, -81, -5	4.0052
Occipital lobe (Fusiform Face Area)	Right	42, -86, -8	3.93463
<i>Healthy controls - Deactivations</i>			
Posterior cingulate gyrus	Left	-4, -31, 26	3.9956
Posterior cingulate gyrus	Right	6, -33, 28	3.9061
Superior parietal gyrus	Left	-12, -61, 44	3.3147
Superior parietal gyrus	Right	12, -70, 40	3.6446
Occipital lobe	Left	-30, -82, 24	3.7414
Occipital lobe	Right	40, -84, 24	3.3893
Pre-subgenual frontal cortex	Left	-10, 26, -12	4.4617
Pre-subgenual frontal cortex	Right	8, 28, -10	4.6346
<i>First-degree relatives - Deactivations</i>			
Superior temporal gyrus	Left	-64, -23, 4	3.7838
Superior temporal gyrus	Right	59, -28, 8	5.0942
Middle inferior temporal gyrus	Left	-54, -12, -16	2.5841
Middle inferior temporal gyrus	Right	54, -20, -16	4.0745
Precentral gyrus	Left	-11, -32, 66	3.3799
Precentral gyrus	Right	2, -28, 66	3.6165
Postcentral gyrus	Left	-14, -32, 68	3.5393
Postcentral gyrus	Right	34, -32, 52	3.6572
Subgenual frontal cortex	Left	1, 22, -12	3.5019
Subgenual frontal cortex	Right	-12, 22, -14	3.4752
Parahippocampal gyrus	Left	-22, -30, -22	4.4278
Parahippocampal gyrus	Right	34, -21, -22	3.3432

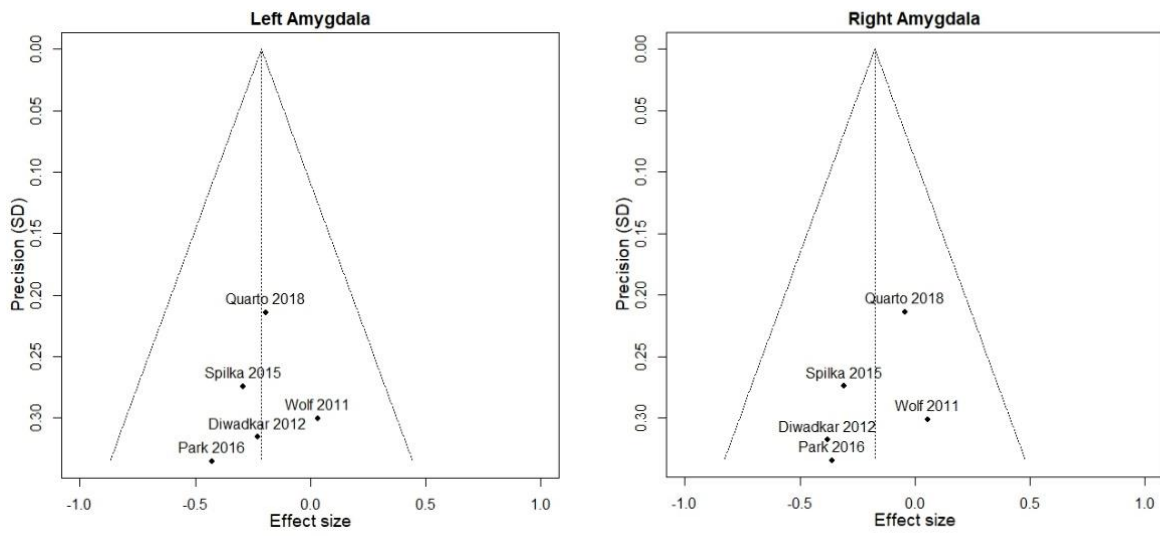
Brain region	Hemisphere	MNI (x,y,z)	SDM-Z
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Table S4. MNI coordinates of between-group meta-analysis. We employed the Hammersmith brain atlas (n30r83, © Copyright Imperial College of Science, Technology and Medicine 2007. All rights reserved⁶¹) in order to determine the name of brain structures.

Brain region	Hemisphere	MNI (x,y,z)	SDM-Z
<i>First-degree relatives < Healthy controls</i>			
Hippocampus	Left	-26, -22, -12	-2.8437
Parahippocampal gyrus	Left	-20, -18, -20	-2.8497
Hippocampus	Right	28, -12, -16	-3.141
Insula	Left	-40, -10, 8	-3.96045
Insula	Right	64, 20, -4	-2.423
Putamen	Left	-17, 4, -9	-2.60312
Amygdala	Right	28, 0, -26	-2.8438
Amygdala	Left	-22, -4, -24	-2.18346
Inferiolateral parietal lobe	Left	-46, -52, 28	-2.6742
Inferiolateral parietal lobe	Right	52, -27, 39	-2.10457
Superior parietal gyrus	Right	8, -52, 68	-3.47912
Superior parietal gyrus	Left	-22, -52, 62	-2.34547
Cerebellum	Left	-18, -48, -32	-2.85079
Cerebellum	Right	16, -36, -34	-2.2929
Inferior frontal gyrus	Right	52, 22, 12	-2.36139
Precentral gyrus	Right	2, -24, 68	-3.25278
Precentral gyrus	Left	-16, -24, 74	-2.70431
Postcentral gyrus	Left	-10, -30, 76	-2.79808
Postcentral gyrus	Right	8, -31, 76	-2.76954
Posterior cingulate gyrus	Left	-10, -22, 40	-2.41395
Posterior cingulate gyrus	Right	10, -7, 42	-2.37083

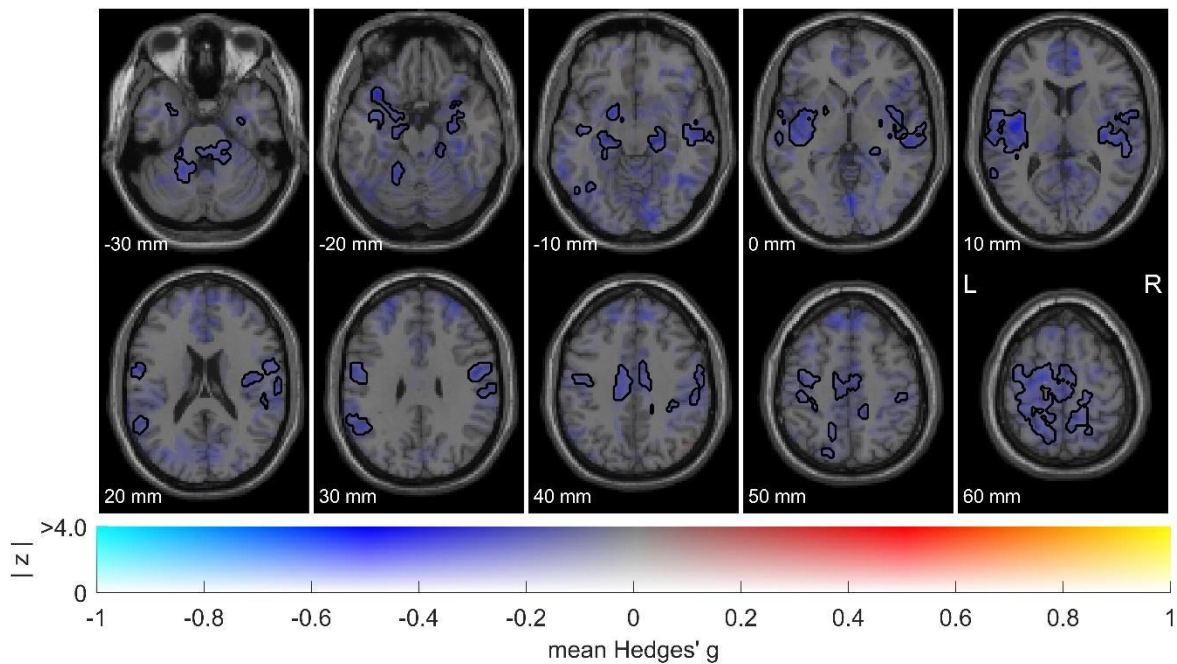


Supplementary Figure S1. Forest plots depicting the mean \pm variance of effect sizes for group comparison in the left and right amygdala (defined using the Melbourne Subcortex Atlas⁶²). The black diamonds represent the overall effect size.



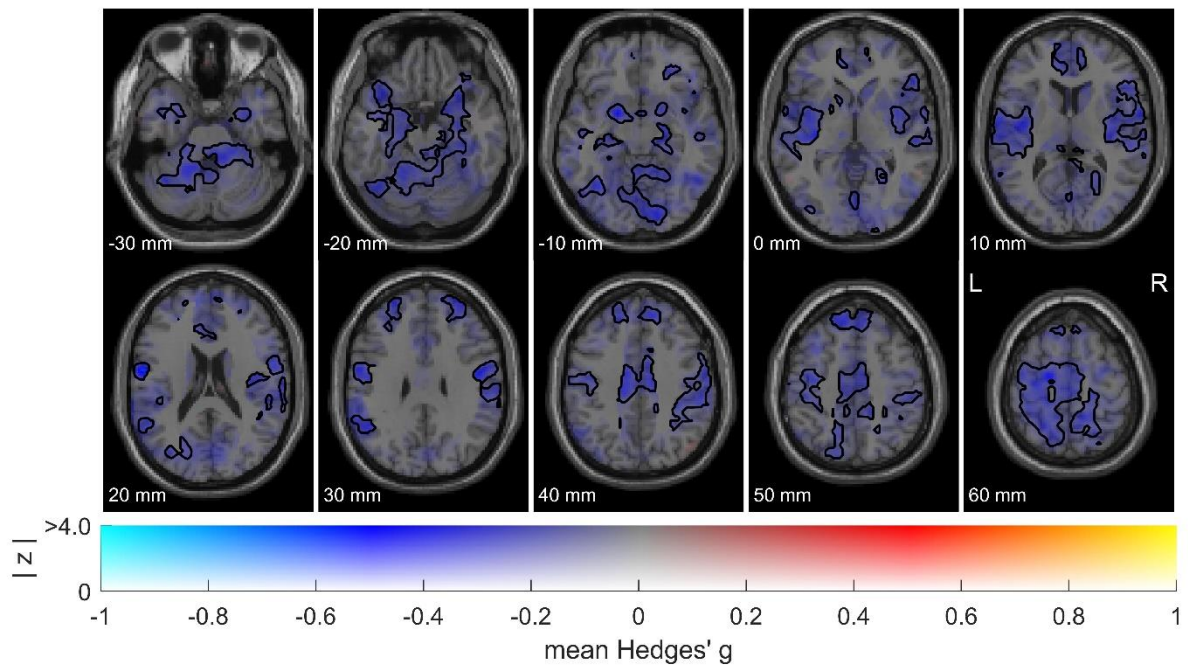
Supplementary Figure S2. Funnel plots in left and right amygdala. The symmetrical distribution of studies suggests no evidence for publication bias.

First-degree relatives > Healthy controls



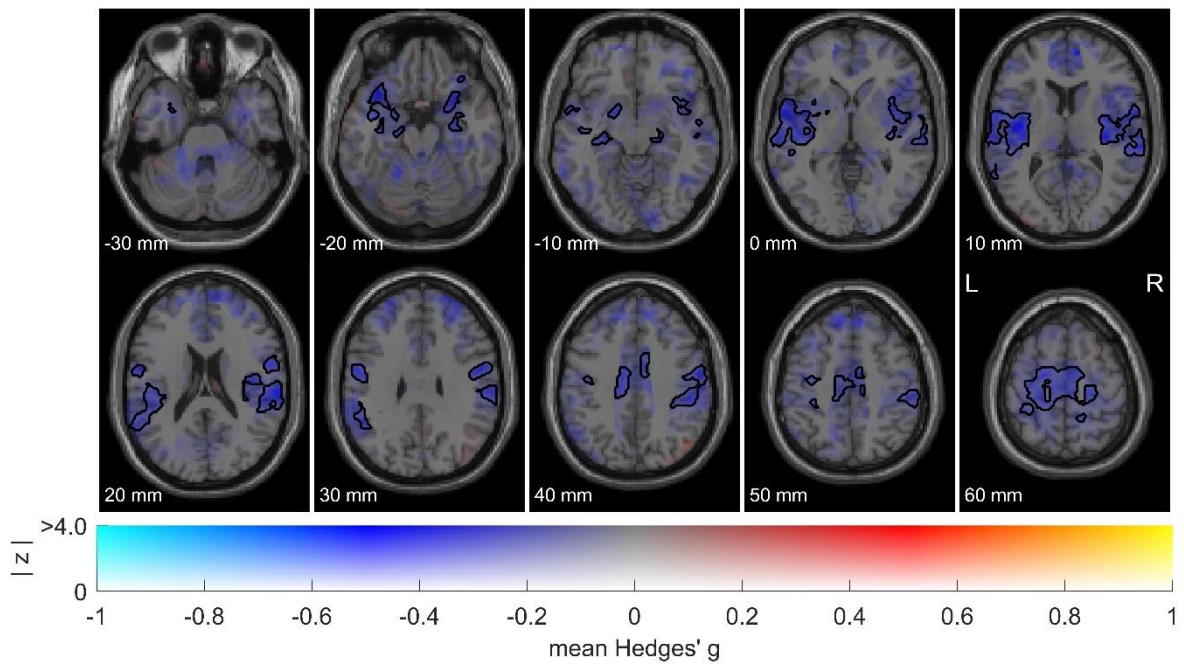
Supplementary Figure S3. Combined image- and coordinate-based between-group meta-analysis of functional neuroimaging studies investigating brain responses to neutral faces in healthy first-degree relatives of patients with schizophrenia versus healthy controls ($n = 7$ studies; 157 first-degree relatives and 207 healthy controls). *These are dual-coded images^{63,64} in which color represents mean Hedges' g (brain regions showing activations are depicted in red while deactivations are depicted in blue), and transparency represents z -values. Black line contours denote significant (de-)activations at $p_{TFCE} < 0.05$.*

First-degree relatives > Healthy controls



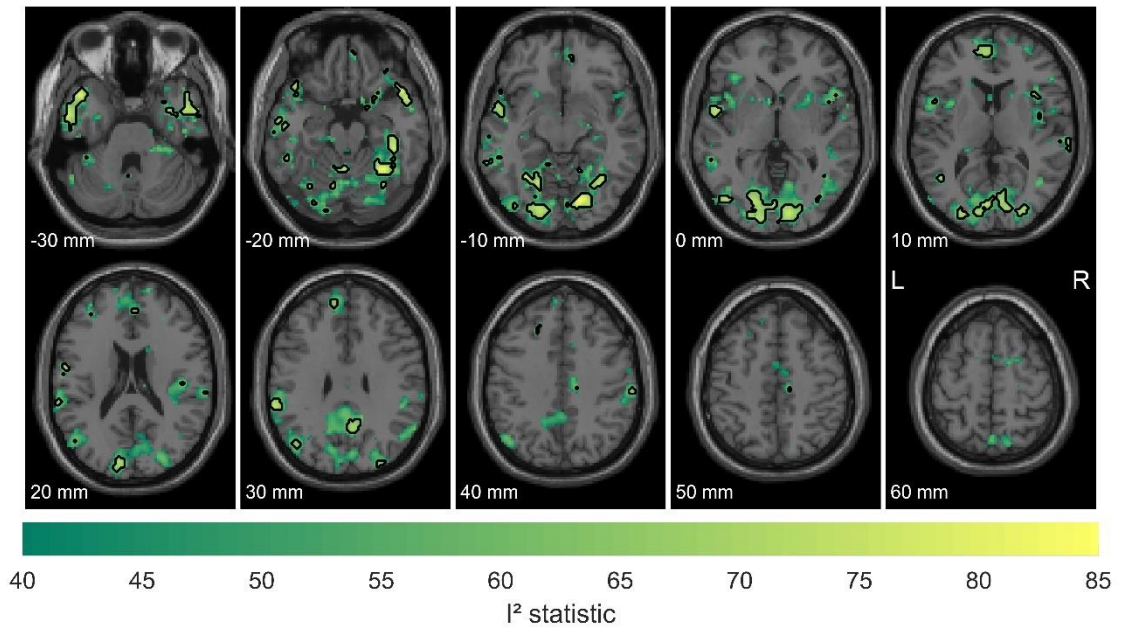
Supplementary Figure S4. Meta-analysis without studies with partial brain coverage (1 study excluded⁶⁰, $n = 4$ studies; 100 first-degree relatives and 125 healthy controls). *These are dual-coded images^{63,64} in which color represents mean Hedges' g (brain regions showing activations are depicted in red while deactivations are depicted in blue), and transparency represents z-values. Black line contours denote significant (de-)activations at $p_{TFCE} < 0.05$.*

First-degree relatives > Healthy controls



Supplementary Figure S5. Meta-analysis (with mean age and quality of the study as covariates) of functional neuroimaging studies investigating brain responses to neutral faces in healthy first-degree relatives of patients with schizophrenia versus healthy controls (n = 5 studies; 120 first-degree relatives and 150 healthy controls). These are dual-coded images^{63,64} in which color represents mean Hedges' g (brain regions showing activations are depicted in red while deactivations are depicted in blue), and transparency represents z-values. Black line contours denote significant (de-)activations at $p_{TFCE} < 0.05$.

First-degree relatives > Healthy controls



Supplementary Figure S6. Whole-brain heterogeneity map. Heterogeneity map displaying for each voxel the I^2 statistic. Since an I^2 statistic lower than 40% is commonly interpreted as low heterogeneity⁶⁵, the map was thresholded at $I^2 > 40\%$. Black line contours denote clusters showing at least substantial heterogeneity ($I^2 > 60\%$).

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SUPPLEMENTARY INFORMATION

Molecular mapping of a core transcriptional signature of microglia-specific genes in schizophrenia

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Supplementary Methods

Microglia genes

The present study exclusively included genes that are part of a core transcriptional signature of human microglia [1]. This signature was established by Patir and colleagues through the identification of co-expressed genes associated with microglia, ensuring their presence in at least three out of nine distinct human datasets of microglia.

Among these genes, we only included microglia genes previously shown to be transcriptionally altered in SZ. We identified these genes according to three criteria.

Firstly, we selected the following genes whose expression was found to be altered in at least one study included in the meta-analysis conducted by Snijders et al. [2] (which explored the expression of 8 genes in total): *AIF1* (Hedges' $g = -1.324$, p -value = 0.003), *CD68* (Hedges' $g = -0.845$, p -value = 0.028), *CSF1R* (Hedges' $g = -0.874$, p -value = 0.023), *HLA-DRB4* (Hedges' $g = -1.403$, p -value = 0.014).

Secondly, we selected the following genes that were transcriptionally altered both in a postmortem study exploring 16 microglia genes from Snijders et al. [2] (*CSF1R* ($\text{Log}_2\text{FC} = -3.306$, adj p -value = <0.05), *IRF8* ($\text{Log}_2\text{FC} = -2.945$, adj p -value = <0.05), *ITGAX* ($\text{Log}_2\text{FC} = -2.535$, adj p -value = <0.05), *OLR1* ($\text{Log}_2\text{FC} = -5.500$, adj p -value = <0.05), *TMEM119* ($\text{Log}_2\text{FC} = -6.532$, adj p -value = <0.05)) and in the largest transcriptomic study in schizophrenia investigating the expression of 25774 genes, from Gandal et al. [3] (*CSF1R* ($\text{Log}_2\text{FC} = -0.176$, adj p -value = <0.05), *IRF8* ($\text{Log}_2\text{FC} = -0.229$, adj p -value = <0.05), *ITGAX* ($\text{Log}_2\text{FC} = -0.305$, adj p -value = <0.05), *OLR1* ($\text{Log}_2\text{FC} = -0.215$, adj p -value = <0.05), *TMEM119* ($\text{Log}_2\text{FC} = -0.237$, adj p -value = <0.05)): *CSF1R*, *IRF8*, *ITGAX*, *OLR1*, *TMEM119*.

Thirdly, we selected the following genes that consistently exhibited differential expression in individuals with schizophrenia compared with healthy controls in a meta-analysis conducted by Bergon and collaborators [4] which explored the expression of 8655 genes in postmortem brain tissues (*CX3CR1* ($\text{FC} = -1.24$, adj p -value = < 0.001), *NCF4* ($\text{FC} = 1.06$, adj p -value = 0.0005), *TLR2* ($\text{FC} = 1.12$, adj p -value = 0.00013), *TSPO* ($\text{FC} = 1.10$, adj p -value = 0.0006)), as well as 16661 genes in peripheral tissues (*CX3CR1* ($\text{FC} = -1.19$, adj p -value = 0.0019), *NCF4* ($\text{FC} = 1.13$, adj p -value = 0.017),

TLR2 (FC = 1.16, adj p-value = 0.0007), *TSPO* (FC = 1.12, adj p-value = 0.012): *CX3CR1*, *NCF4*, *TLR2*.

HLA-DRB4 was not included due to the lack of specificity of the microarray probes, and *TSPO* was omitted as its relevance as a microglia marker has been questioned [5] with evidence suggesting a closer association with astrocytes [6].

Eventually, it should be noted that the genes included in this study exceeded the minimum requirement of being present in three datasets, as established by Patir et al. when defining the core transcriptional signature of human microglia [1]. Indeed, our candidate genes were present in a larger number of datasets, specifically in at least six out of the nine co-expression derived datasets, thus reinforcing their strong association with microglia. Additionally, it is noteworthy that all the genes included in this study were also identified in a recently published list of microglia signature genes that are highly expressed in bulk brain tissues [7].

Inclusion of datasets

Since our primary aim was to map transcriptional alterations of microglia genes in brain and peripheral tissues samples, one dataset per brain region (or peripheral tissue) was selected. When more than one dataset from the same brain region (or peripheral tissue) was available, we selected the one that would maximize the following 2 criteria in this particular order of relevance: 1) the dataset is capable to explore the largest number of genes from our list of candidate genes; 2) the dataset has the largest number of subjects. Based on these criteria, 2 datasets (GSE21138 from Narayan et al., 2008 [8]; GSE38481 from de Jong et al., 2012 [9]) from the list of 12 eligible datasets were not included in the main analyses.

Datasets included

It should be noted that the datasets included in this study are slightly different from those that were pre-registered on AsPredicted.org (#67610, <https://aspredicted.org/285rn.pdf>). This is due to the following reasons: 1) we initially planned to include datasets using three types of Affymetrix arrays (HG-U133_Plus_2, Human Gene 1.0 ST or Human Gene 1.1 ST) which could technically interrogate our

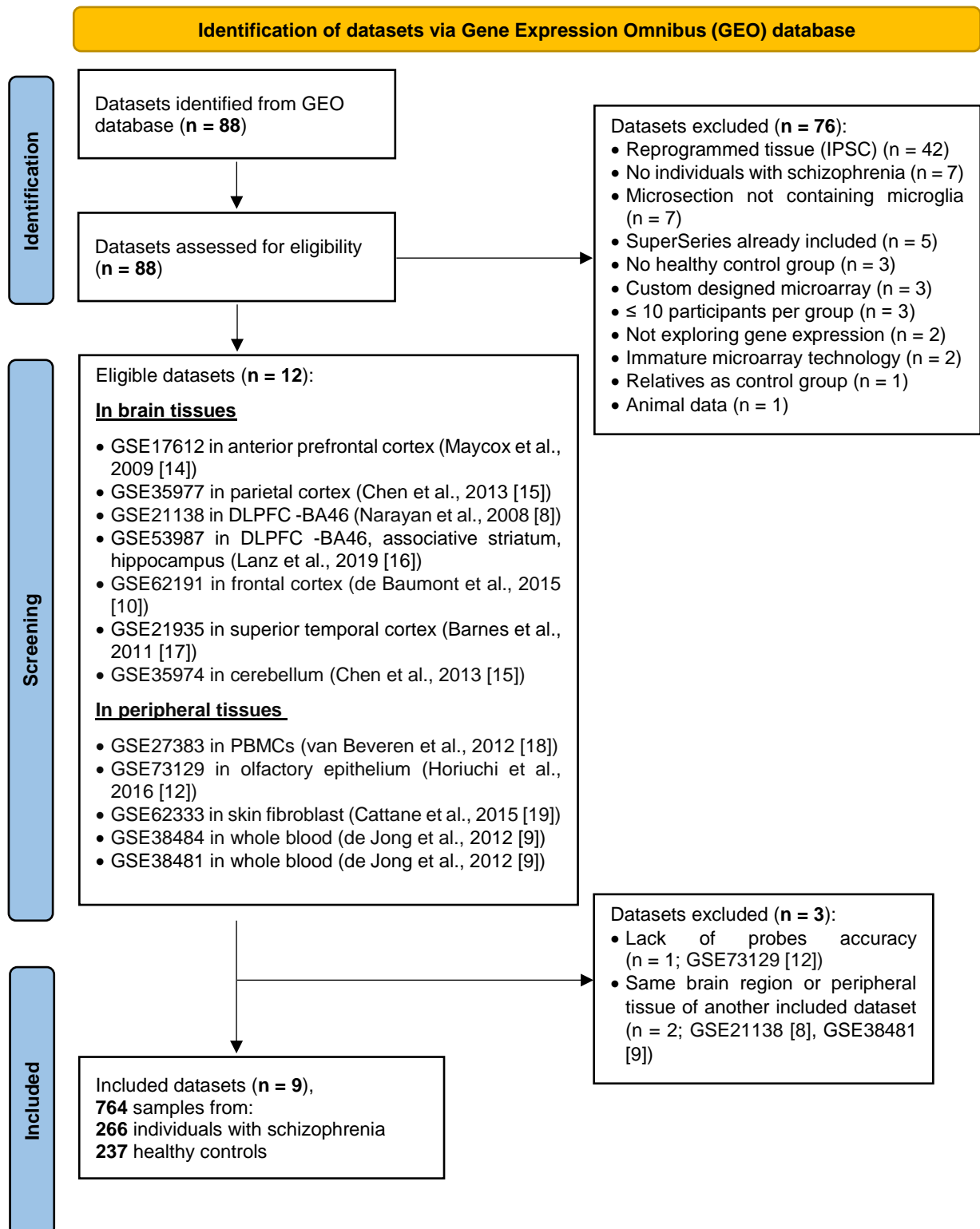
list of candidate genes. However, this criterion precluded the inclusion of other array platforms capable of exploring these candidate genes (such as Agilent or Illumina arrays). Therefore, this criterion was removed, and only custom-designed microarrays were excluded. Consequently, an additional non pre-registered dataset was included in this study (GSE62191 from de Baumont et al., 2015 [10]); 2) we excluded one pre-registered dataset (GSE93987 from Arion et al., 2015 [11] since it was captured through a laser microdissection of pyramidal cells, and thus did not contain microglia cells violating our inclusion criteria; 3) we also excluded one pre-registered dataset (GSE73129 from Horiuchi et al., 2016 [12]) due to lack of probe accuracy of at least half of the candidate genes (i.e., 5 genes present a lack of variability in gene expression values for all participants, probably reflecting transcriptional noise).

Following this selection, we report results from 9 different datasets. Finally, it should be noted that for two included datasets, we could not reliably measure the expression of a few genes (*CD68* and *ITGAX* in the superior temporal cortex; *NCF4* and *TMEM119* in the frontal cortex) due to a lack of probe accuracy for those genes. The presently reported non-significant differences between individuals with schizophrenia and healthy controls for those latter genes in the relevant datasets should therefore be considered with caution.

Bayesian analyses

In additional Bayesian analyses, we quantify evidence in favor of the null (H_0) and alternative (H_1) hypotheses using the Bayes Factor (BF). Indeed, BFs are the ratio of the likelihood of the data under the alternative hypothesis and under the null hypothesis. BF_{10} quantifies the evidence in favor of H_1 compared with H_0 , while BF_{01} ($= 1/BF_{10}$) quantifies the evidence in favor of H_0 compared with H_1 . Conventionally a BF_{10} (or BF_{01}) that exceeds the threshold of 3 represents moderate evidence in favor of H_1 (or H_0), while when it exceeds the threshold of 100 the evidence can be considered as decisive. Finally, it is not possible to conclude regarding the presence or absence of group differences when BF_{10} (or BF_{01}) is between 1 and 3 (i.e., anecdotal evidence) [13].

Supplementary Figure 1. Flow Chart outlining the selection procedure of GEO datasets



Abbreviations: GEO, Gene Expression Omnibus; iPSC, induced pluripotent stem cells; DLPFC, dorsolateral prefrontal cortex; BA, Brodmann area; PBMCs, peripheral blood mononuclear cells

Supplementary Table 1. Descriptive Statistics of Log2 (gene expression) values in brain and peripheral tissues

		Anterior prefrontal cortex (GSE17612)																							
		Log2(AIF1)		Log2(CD68)		Log2(CSF1R)		Log2(CX3CR1)		Log2(IRF8)		Log2(ITGAX)		Log2(NCF4)		Log2(OLR1)		Log2(TLR2)		Log2(TMEM119)					
		HC	SZ	HC	SZ	HC	SZ	HC	SZ	HC	SZ	HC	SZ	HC	SZ	HC	SZ	HC	SZ	HC	SZ	HC	SZ		
Valid		23	28	23	28	23	28	23	28	23	28	23	28	23	28	23	28	23	28	23	28	23	28		
Missing		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
Mean		4.21	4.74	3.78	3.68	7.99	8.22	8.06	8.27	6.47	6.78	5.47	5.65	5.91	5.88	6.47	6.57	5.30	6.01	5.79	5.79	6.09	6.09		
SD		0.58	1.09	0.90	0.89	0.58	0.51	0.89	0.86	0.51	0.48	0.88	0.58	0.59	0.62	0.37	0.57	1.42	1.32	0.56	0.56	0.44	0.44		
Normality		No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes		
Homoscedasticity		No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes		
Max		6.24	7.06	5.74	6.04	9.11	9.10	9.23	9.79	7.41	7.58	6.83	6.70	6.85	6.78	7.27	9.01	7.47	8.00	6.85	6.85	7.05	7.05		
Min		3.68	3.31	2.48	2.40	6.72	7.36	6.18	5.99	5.68	5.80	3.65	4.22	4.14	4.01	5.46	5.95	1.80	2.82	4.62	4.62	4.92	4.92		
		Parietal cortex (GSE35977)																							
		Log2(AIF1)		Log2(CD68)		Log2(CSF1R)		Log2(CX3CR1)		Log2(IRF8)		Log2(ITGAX)		Log2(NCF4)		Log2(OLR1)		Log2(TLR2)		Log2(TMEM119)					
		HC	SZ	HC	SZ	HC	SZ	HC	SZ	HC	SZ	HC	SZ	HC	SZ	HC	SZ	HC	SZ	HC	SZ	HC	SZ		
Valid		50	51	50	51	50	51	50	51	50	51	50	51	50	51	50	51	50	51	50	51	50	51		
Missing		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
Mean		6.60	6.44	7.15	7.08	7.69	7.55	7.32	7.04	7.14	6.99	6.46	6.34	5.61	5.58	7.11	6.67	5.97	6.04	6.55	6.55	6.47	6.47		
SD		0.49	0.43	0.48	0.40	0.49	0.47	0.85	0.72	0.50	0.45	0.30	0.24	0.20	0.23	0.63	0.38	0.57	0.47	0.22	0.22	0.17	0.17		
Normality		No	Yes	No	No	No	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes		
Homoscedasticity		Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes		
Max		8.80	7.59	9.14	8.38	9.59	8.54	9.14	8.45	9.13	8.53	7.81	6.92	6.26	6.27	9.28	7.66	9.18	7.87	7.09	7.09	6.88	6.88		
Min		5.89	5.32	6.69	6.47	6.89	6.42	5.69	5.61	6.19	6.17	6.04	5.87	5.24	5.17	5.74	5.82	5.40	5.54	6.14	6.14	6.01	6.01		

Superior Temporal cortex (GSE21935)																							
		Log2(AIF1)		Log2(CD68)		Log2(CSF1R)		Log2(CX3CR1)		Log2(IRF8)		Log2(ITGAX)		Log2(NCF4)		Log2(OLR1)		Log2(TLR2)		Log2(TMEM119)			
		HC	SZ	HC	SZ	HC	SZ	HC	SZ	HC	SZ	HC	SZ	HC	SZ	HC	SZ	HC	SZ	HC	SZ		
Valid		13	18	3	2	19	23	19	23	19	23	5	9	17	23	19	23	19	22	19	23		
Missing		6	5	16	21	0	0	0	0	0	0	14	14	2	0	0	0	0	1	0	0		
Mean		3.78	3.31	1.57	1.98	6.74	7.16	7.54	7.27	7.54	5.63	3.35	2.78	4.19	4.61	5.42	5.63	4.28	5.13	3.95	4.28		
SD		1.25	1.15	2.05	0.60	0.76	0.85	0.79	1.13	1.13	0.96	1.31	2.10	0.67	0.59	0.53	0.68	1.15	0.98	1.21	1.38		
Normality		Yes	Yes	NA	NA	Yes	Yes	Yes	Yes	Yes	Yes	NA	NA	Yes	Yes	No	No	Yes	Yes	Yes	No		
Homoscedasticity		Yes	Yes	NA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	NA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes		
Max		5.27	5.09	3.78	2.40	8.73	8.53	9.16	9.32	6.74	6.74	4.43	4.71	5.16	5.64	6.13	7.76	6.05	6.40	6.32	5.99		
Min		0.97	1.07	-0.27	1.55	5.34	5.27	5.66	5.58	2.40	3.49	1.59	-1.15	2.98	3.72	4.19	4.62	1.11	2.91	1.18	0.81		
Associative striatum (GSE53987)																							
		Log2(AIF1)		Log2(CD68)		Log2(CSF1R)		Log2(CX3CR1)		Log2(IRF8)		Log2(ITGAX)		Log2(NCF4)		Log2(OLR1)		Log2(TLR2)		Log2(TMEM119)			
		HC	SZ	HC	SZ	HC	SZ	HC	SZ	HC	SZ	HC	SZ	HC	SZ	HC	SZ	HC	SZ	HC	SZ		
Valid		18	18	18	18	18	18	18	18	18	18	18	18	18	18	18	18	18	18	18	18		
Missing		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
Mean		6.21	6.25	7.37	7.45	9.06	8.89	8.01	7.31	7.61	7.73	7.24	7.16	6.98	7.06	7.89	7.22	6.89	7.01	6.71	6.50		
SD		0.26	0.34	0.15	0.17	0.38	0.54	0.75	0.73	0.29	0.38	0.17	0.20	0.09	0.29	0.61	0.65	0.29	0.54	0.29	0.41		
Normality		Yes	Yes	Yes	No	Yes	Yes	No	No	Yes	No	Yes	Yes	Yes	No	Yes	Yes	No	No	Yes	Yes		
Homoscedasticity		Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes		
Max		6.91	6.72	7.64	7.94	9.63	10.28	8.87	8.43	8.16	8.84	7.58	7.54	7.15	7.97	8.73	8.51	7.89	9.06	7.22	7.53		
Min		5.73	5.59	7.11	7.26	8.37	7.94	6.24	6.21	7.20	7.03	6.90	6.69	6.79	6.62	6.45	5.98	6.55	6.67	6.34	5.80		

Hippocampus (GSE53987)

	Log2(AIF1)		Log2(CD68)		Log2(CSF1R)		Log2(CX3CR1)		Log2(IRF8)		Log2(ITGAX)		Log2(NCF4)		Log2(OLR1)		Log2(TLR2)		Log2(TMEM119)	
	HC	SZ	HC	SZ	HC	SZ	HC	SZ	HC	SZ	HC	SZ	HC	SZ	HC	SZ	HC	SZ	HC	SZ
Valid	18	15	18	15	18	15	18	15	18	15	18	15	18	15	18	15	18	15	18	15
Missing	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Mean	3.61	3.60	5.10	5.24	7.47	7.25	5.85	4.87	5.92	5.92	5.45	5.24	4.24	4.38	5.36	4.89	5.39	5.72	4.03	3.95
SD	0.24	0.20	0.23	0.18	0.42	0.85	0.50	0.818	0.30	0.60	0.25	0.36	0.20	0.48	0.45	0.97	0.39	1.06	0.21	0.53
Normality	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No	Yes	No	Yes	Yes
Homoscedasticity	Yes	Yes	Yes	Yes	No	No	No	No	No	No	Yes	Yes	No	No	No	No	No	No	No	No
Max	4.04	4.00	5.63	5.58	8.37	8.59	6.53	6.37	6.37	7.38	6.04	6.02	4.63	5.50	6.51	7.77	6.38	8.31	4.34	4.84
Min	3.21	3.26	4.70	5.01	6.79	6.08	4.68	3.68	5.32	5.07	5.17	4.68	3.75	3.81	4.78	4.04	4.91	4.90	3.66	3.19

DLPFC (GSE53987)

	Log2(AIF1)		Log2(CD68)		Log2(CSF1R)		Log2(CX3CR1)		Log2(IRF8)		Log2(ITGAX)		Log2(NCF4)		Log2(OLR1)		Log2(TLR2)		Log2(TMEM119)	
	HC	SZ	HC	SZ	HC	SZ	HC	SZ	HC	SZ	HC	SZ	HC	SZ	HC	SZ	HC	SZ	HC	SZ
Valid	19	15	19	15	19	15	19	15	19	15	19	15	19	15	19	15	19	15	19	15
Missing	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Mean	3.53	3.46	4.93	5.00	7.25	7.12	5.53	5.05	5.89	5.76	4.68	4.58	4.54	4.57	5.76	5.52	5.00	5.40	3.88	3.93
SD	0.16	0.23	0.16	0.19	0.49	0.63	0.53	0.49	0.39	0.57	0.17	0.18	0.18	0.24	0.40	0.37	0.25	0.86	0.32	0.47
Normality	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Homoscedasticity	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes
Max	3.87	3.90	5.22	5.27	8.08	8.53	6.24	5.74	6.64	7.55	4.94	4.81	4.94	5.23	6.52	6.24	5.64	7.50	4.51	5.05
Min	3.23	3.08	4.70	4.74	6.45	6.08	4.30	4.27	5.31	5.20	4.19	4.24	4.18	4.19	4.89	5.05	4.53	4.77	3.29	3.21

Frontal cortex (GSE62191)																					
	Log2(AIF1)		Log2(CD68)		Log2(CSF1R)		Log2(CX3CR1)		Log2(IRF8)		Log2(ITGAX)		Log2(NCF4)		Log2(OLR1)		Log2(TLR2)		Log2(TMEM119)		
	HC	SZ	HC	SZ	HC	SZ	HC	SZ	HC	SZ	HC	SZ	HC	SZ	HC	SZ	HC	SZ	HC	SZ	
Valid	30	29	30	29	29	29	30	29	30	28	30	28	30	29	30	29	30	29	30	29	/
Missing	0	0	0	0	1	0	0	0	0	1	0	1	0	0	0	0	0	0	0	0	/
Mean	3.10	3.11	1.86	1.86	3.53	3.61	2.84	2.91	1.18	1.18	1.21	1.05	1.79	1.67	1.76	1.83	1.76	1.83	1.76	1.83	/
SD	0.35	0.24	0.34	0.26	0.37	0.30	0.51	0.39	0.33	0.20	0.30	0.25	0.32	0.22	0.47	0.37	0.47	0.37	0.47	0.37	/
Normality	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	No	Yes	/
Homoscedasticity	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	/
Max	3.84	3.58	2.60	2.62	4.19	4.08	3.77	3.58	1.98	1.51	1.82	1.49	2.69	2.01	3.05	2.68	3.05	2.68	3.05	2.68	/
Min	2.55	2.40	1.16	1.43	2.68	2.55	1.87	1.66	0.82	0.84	0.76	0.74	1.21	1.09	0.97	1.06	0.97	1.06	0.97	1.06	/
Cerebellum (GSE35974)																					
	Log2(AIF1)		Log2(CD68)		Log2(CSF1R)		Log2(CX3CR1)		Log2(IRF8)		Log2(ITGAX)		Log2(NCF4)		Log2(OLR1)		Log2(TLR2)		Log2(TMEM119)		
	HC	SZ	HC	SZ	HC	SZ	HC	SZ	HC	SZ	HC	SZ	HC	SZ	HC	SZ	HC	SZ	HC	SZ	
Valid	50	44	50	44	50	44	50	44	50	44	50	44	50	44	50	44	50	44	50	44	44
Missing	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Mean	6.70	6.48	7.32	7.19	7.48	7.33	6.93	6.81	7.57	7.33	6.53	6.44	6.11	6.11	5.67	5.51	5.99	5.93	5.99	5.93	7.00
SD	0.36	0.27	0.30	0.14	0.26	0.23	0.52	0.44	0.38	0.46	0.19	0.13	0.17	0.12	0.34	0.24	0.29	0.22	0.29	0.22	0.15
Normality	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	No	Yes	No
Homoscedasticity	Yes	No	No	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Max	7.71	7.08	8.87	7.54	7.98	7.92	8.01	7.69	8.22	8.19	6.93	6.74	6.52	6.39	6.58	6.01	7.39	6.46	7.39	6.46	7.19
Min	5.84	5.97	6.98	6.97	7.05	6.73	5.88	5.99	6.53	6.56	6.11	6.14	5.84	5.89	5.17	5.03	5.58	5.49	5.58	5.49	6.71

Blood -whole blood (GSE38484)

	Log2(AIF1)		Log2(CD68)		Log2(CSF1R)		Log2(CX3CR1)		Log2(IRF8)		Log2(ITGAX)		Log2(NCF4)		Log2(OLR1)		Log2(TLR2)		Log2(TMEM119)	
	HC	SZ	HC	SZ	HC	SZ	HC	SZ	HC	SZ	HC	SZ	HC	SZ	HC	SZ	HC	SZ	HC	SZ
Valid	96	106	96	106	96	106	96	106	96	106	96	106	96	106	96	106	96	106	96	106
Missing	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Mean	11.25	11.44	11.01	10.82	11.18	10.95	8.69	8.45	10.48	10.65	10.80	10.66	8.96	8.94	7.57	7.70	8.15	8.29	7.50	7.47
SD	0.46	0.43	0.39	0.39	0.37	0.41	0.34	0.30	0.39	0.41	0.34	0.53	0.34	0.37	0.12	0.30	0.30	0.30	0.12	0.09
Normality	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No	Yes	Yes	No	Yes
Homoscedasticity	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No	No	Yes	Yes	No	Yes
Max	12.02	12.69	12.05	11.95	12.26	11.90	9.57	9.11	11.30	11.67	11.65	11.80	9.92	9.81	8.16	9.02	8.78	9.10	8.09	7.75
Min	9.70	10.23	9.85	9.86	10.40	9.86	8.04	7.90	9.53	9.64	9.99	8.98	8.39	8.15	7.41	7.40	7.47	7.65	7.30	7.28

Blood -PBMCs (GSE27383)

	Log2(AIF1)		Log2(CD68)		Log2(CSF1R)		Log2(CX3CR1)		Log2(IRF8)		Log2(ITGAX)		Log2(NCF4)		Log2(OLR1)		Log2(TLR2)		Log2(TMEM119)	
	HC	SZ	HC	SZ	HC	SZ	HC	SZ	HC	SZ	HC	SZ	HC	SZ	HC	SZ	HC	SZ	HC	SZ
Valid	29	43	29	43	29	43	29	43	29	43	29	43	29	43	29	43	29	43	29	43
Missing	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Mean	4.65	4.64	8.57	8.63	10.66	10.61	13.51	13.34	11.66	11.71	8.87	8.89	9.26	9.35	4.23	4.34	10.71	10.93	3.79	3.88
SD	0.11	0.15	0.31	0.44	0.29	0.34	0.29	0.26	0.22	0.18	0.22	0.28	0.34	0.35	0.32	0.57	0.36	0.45	0.13	0.15
Normality	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes	Yes
Homoscedasticity	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Max	4.87	5.24	9.42	9.49	11.11	11.24	14.05	13.73	12.00	12.21	9.34	9.39	9.72	10.05	5.57	6.81	11.26	12.02	4.04	4.28
Min	4.39	4.36	8.08	7.17	10.18	9.45	12.94	12.38	11.21	11.30	8.52	8.03	8.57	8.54	3.91	3.84	9.83	9.72	3.53	3.60

Skin fibroblast (GSE62333)

	Log2(AIF1)		Log2(CD68)		Log2(CSF1R)		Log2(CX3CR1)		Log2(IRF8)		Log2(ITGAX)		Log2(NCF4)		Log2(OLR1)		Log2(TLR2)		Log2(TMEM119)	
	HC	SZ	HC	SZ	HC	SZ	HC	SZ	HC	SZ	HC	SZ	HC	SZ	HC	SZ	HC	SZ	HC	SZ
Valid	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20
Missing	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Mean	3.04	3.10	9.52	9.49	4.14	4.07	3.75	3.71	3.33	3.37	3.76	3.718	4.355	4.310	5.564	5.677	2.986	3.023	9.453	9.765
SD	0.10	0.16	0.72	0.51	0.23	0.18	0.22	0.35	0.30	0.30	0.177	0.123	0.156	0.192	1.009	1.011	0.093	0.128	0.473	0.468
Normality	Yes	Yes	No	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Homoscedasticity	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Max	3.26	3.42	10.27	10.50	4.55	4.38	4.31	4.98	3.95	3.96	4.054	4.017	4.567	4.609	7.745	7.346	3.183	3.399	10.398	10.597
Min	2.85	2.89	7.70	8.71	3.81	3.63	3.43	3.40	2.94	2.87	3.365	3.535	3.973	3.910	3.806	3.877	2.826	2.783	8.272	8.804

Abbreviations: HC, healthy controls; SZ, individuals with schizophrenia; SD, Standard deviation; DLPFC, dorsolateral prefrontal cortex; PBMCs, Peripheral blood mononuclear cells

Supplementary Table 2. Description of the original studies from which the datasets were obtained

GEO Accession Number	Tissue	Region / Cell Type	Microarray	SZ	HC	Description of the original study
GSE53987	Brain	DLPFC (BA46)	HG-U133_Plus_2	15	19	<p>Sample collection: University of Pittsburgh brain bank</p> <p>Consent / Ethics: Brain specimens were obtained during autopsies after consent for donation was obtained from the next-of-kin. All procedures were approved by the University of Pittsburgh Committee for the Oversight of Research and Clinical Trials Involving the Dead and the Institutional Review Board for Biomedical Research</p> <p>SZ: Diagnoses were made by an independent committee of experienced research clinicians, using DSM-IV criteria and based on the results of structured interviews conducted with family members and review of medical records</p> <p>Healthy controls: The absence of psychiatric diagnoses was confirmed using an identical approach. The healthy controls were free of any neurological or psychiatric illness during their life course</p> <p>Original study: Lanz <i>et al.</i>, Translational Psychiatry, 2019 (PMID: 31123247)</p> <p>Objective: To evaluate shared transcriptional alterations across connected brain regions in SZ, bipolar disorder (BD), major depressive disorder (MDD) individuals, or HC</p> <p>Methods: Genome-wide expression was obtained from postmortem DLPFC, hippocampus, and associative striatum from 19 well-matched tetrads of SZ, BD, MDD, or HC</p> <p>Main results: SZ showed a substantial burden of differentially expressed genes across all examined brain regions with the greatest effects in hippocampus, whereas BD and MDD showed less robust alterations. Pathway analysis of transcriptional profiles compared across diagnoses demonstrated commonly enriched pathways between all three disorders in hippocampus, significant overlap between SZ and BD in DLPFC, but no significant overlap of enriched pathways between disorders in striatum. SZ showed increased expression of transcripts associated with inflammation across all brain regions examined, which was not evident in BD or MDD individuals</p>
GSE53987	Brain	Associative striatum	HG-U133_Plus_2	18	18	

GEO Accession Number	Tissue	Region / Cell Type	Microarray	SZ	HC	Description of the original study
GSE35977	Brain	Parietal cortex	HuGene-1_0-st	51	50	<p>Sample collection: Stanley Medical Research Institute's Neuropathology Consortium and Array Collections</p> <p>Consent / Ethics: Specimens were collected with informed consent from next-of-kin</p> <p>SZ: Diagnoses were made by two senior psychiatrists, using DSM-IV criteria and based on medical records and, when necessary, telephone interviews with family members</p> <p>HC: Diagnoses of unaffected controls were based on structured interviews by a senior psychiatrist with family member(s) to rule out Axis I diagnoses.</p> <p>Exclusion criteria: Individuals over age 65 were excluded</p> <p>Original study: Chen <i>et al.</i>, Molecular Psychiatry, 2013 (PMID: 23147385)</p> <p>Objective: To identify schizophrenia-associated gene-expression networks in the parietal cortex and cerebellum of SZ and HC. To test whether the gene modules perturbed in SZ were similarly perturbed in bipolar disorder</p> <p>Methods: Genome-wide expression data was used to construct gene expression networks and identify gene co-expression modules within the networks. The modules were tested for association with SZ. Identified SZ-associated modules were tested for association with bipolar disorder</p> <p>Main results: Two modules were differentially expressed in SZ versus HC. One, upregulated in cerebral cortex, was enriched with neuron differentiation and neuron development genes, as well as disease genome-wide association study genetic signals; the second, altered in cerebral cortex and cerebellum, was enriched with genes involved in neuron protection function. The findings were preserved in five expression datasets, including sets from three brain regions, from a different microarray platform, and from individuals with bipolar disorder</p>
GSE35974	Brain	Cerebellum	HuGene-1_0-st	44	50	

GEO Accession Number	Tissue	Region / Cell Type	Microarray	SZ	HC	Description of the original study
						<p>Sample collection: Tissue collection of the Charing Cross Hospital, Imperial College London, UK</p> <p>Consent / Ethics: All patients with the agreement of their nearest relative or authorized representative, have given written informed consent for use of tissue obtained post-mortem for research. The control group were tissue donors for research from the community. Procedures have been approved by the West London Mental Health Ethical Research Committee and complies with the conditions of the Research Governance Office of the Imperial College of Science, Technology and Medicine Clinical Research Office</p> <p>SZ: All patients met DSM-III diagnostic criteria for chronic residual SZ with pronounced negative symptoms alongside attenuated positive symptoms and intellectual dysfunction. All patients had been treated with neuroleptic drugs except one patient who was neuroleptic naive at death</p> <p>HC: Mentally normal individuals from the community</p> <p>Exclusion criteria: Alzheimer's disease, Parkinson's disease or multiple sclerosis were excluded</p> <p>Original studies: Maycox <i>et al.</i>, Mol Psychiatry, 2009 (PMID: 19255580)</p> <p>Objective: To identify differentially expressed genes in anterior prefrontal cortex (BA 10) from SZ and HC</p> <p>Methods: Genome-wide expression in post-mortem brain tissue from anterior prefrontal cortex (BA 10) was compared between 28 SZ and 23 HC. Results were then compared to those from an independent prefrontal cortex dataset obtained from SZ and HC</p> <p>Main results: 51 gene expression changes were common between the two SZ cohorts, and 49 showed the same direction of disease-associated regulation. Changes were observed in gene sets</p>
GSE17612	Brain	Anterior prefrontal cortex (BA10)	HG-U133_Plus_2	28	23	<p>Original studies: Barnes <i>et al.</i>, J Neurosci Res, 2011 (PMID: 21538462)</p> <p>Objective: Gene ontology pathway enrichment analysis in BA22 and BA10 from SZ and HC</p> <p>Methods: Genome-wide expression was determined in the post-mortem BA22 region of 23 SZ and 19 HC and compared with genome-wide expression of BA10 from the same subjects. Gene ontology pathway enrichment analysis was carried out in each region</p> <p>Main results: In BA22 region, the highest enrichment was observed in processes mediating cell adhesion, synaptic contact, cytoskeletal remodeling, and apoptosis. In BA10 region, the strongest changes were observed in reproductive signaling,</p>
GSE21935	Brain	Superior temporal cortex (BA22)	HG-U133_Plus_2	23	19	

GEO Accession Number	Tissue	Region / Cell Type	Microarray	SZ	HC	Description of the original study
						<p>associated with synaptic vesicle recycling, transmitter release and cytoskeletal dynamics</p> <p>tissue remodeling, and cell differentiation. In SZ, many pathways underpinning synaptic plasticity are disrupted in both BA10 and BA22</p>
						<p>Sample collection: Stanley Medical Research Institute's Neuropathology Consortium</p> <p>Consent / Ethics: The study protocol was approved by the ethics committee of A.C.Camargo Cancer Center and was performed in accordance with the Declaration of Helsinki</p> <p>SZ: Records of all patients were reviewed for DSM-IV psychiatric diagnosis independently by two senior psychiatrists</p> <p>HC: For normal controls, a structured telephone interview with a first-degree family member was carried out in all cases</p> <p>Exclusion criteria: Participants with samples with low RNA integrity were excluded</p> <p>Original study: De Baumont <i>et al.</i>, Schizophrenia Research, 2015 (PMID: 25487697)</p> <p>Objective: To identify the molecular mechanisms that differentiate SZ and individuals with bipolar disorder from healthy controls</p> <p>Methods: Genome-wide expression data were used to identify co-expression of pairs of genes to assess differences between SZ and individuals with bipolar disorder. A Protein-Protein Interaction network was also used to identify additional properties potentially associated with the differentially expressed genes between SZ and individuals with bipolar disorder</p> <p>Main results: Co-expression analyses revealed that the pairs CCR1/SERPINA1, CCR5/HCST, C10A/CD68, CCR5/S100A11 and SERPINA1/TLR1 present the most significant difference between SZ and individuals with BD. Moreover, network analyses showed CASP4, TYROBP, CCR1, SERPINA1, CCR5 and C10A as having a central role in the manifestation of the disease</p>
GSE62191	Brain	Frontal cortex	Agilent 4112F	29	30	

GEO Accession Number	Tissue	Region / Cell Type	Microarray	SZ	HC	Description of the original study
GSE27383	Blood	PBMCs	HG-U133_Plus_2	43	29	<p>Sample collection: Erasmus University Medical Center (EMC), Rotterdam, The Netherlands</p> <p>Consent / Ethics: All subjects provided written informed consent after complete description of the study. For those patients who were too disturbed to provide consent, consent was initially given by a first-degree relative and final written consent was sought within six weeks from the patients themselves. This study was approved by the Erasmus University Medical Center Institutional Review Board and was conducted according to the declaration of Helsinki</p> <p>SZ: Eligible for inclusion were male, stabilized or acutely psychotic, patients diagnosed with SZ or schizophreniform disorder according to DSM IV criteria after a Comprehensive Assessment of Symptoms and History interview (CASH) and by consensus between two senior psychiatrists. Additional criteria were recent onset (defined as duration of illness <5 years) and age (>15 and <36 years)</p> <p>HC: Age-matched controls were recruited from the students and staff of the EMC medical school and hospital</p> <p>Exclusion criteria: For SZ and HC, exclusion criteria were defined as follows: presence of any somatic or neurological disorders and abuse of heroin, cocaine, or alcohol. Cannabis abuse was not an exclusion criterion. Concomitant use of mood-stabilizers and/or antidepressants was an exclusion criterion. For HC, the presence of psychiatric disorders in first-degree relatives was also an exclusion criterion</p> <p>Original study: van Beveren <i>et al.</i>, PLoS ONE, 2012 (PMID: 22393424)</p> <p>Objective: To examine PBMCs expression levels of AKT1 in SZ versus HC, and to examine whether functional biological processes in which AKT1 plays an important role are deregulated in SZ</p> <p>Methods: Genome-wide expression study in the PBMCs of SZ and HC. Functional analysis of biological processes in which AKT1 gene is involved</p> <p>Main results: PBMCs expression of AKT1 was significantly decreased in SZ. 1224 genes were differentially expressed between SZ and controls. Deregulated canonical pathways were involved in cellular processes: immune system, cell adhesion and neuronal</p>

GEO Accession Number	Tissue	Region / Cell Type	Microarray	SZ	HC	Description of the original study
						guidance, neurotrophins and (neural) growth factors, oxidative stress and glucose metabolism, apoptosis and cell-cycle regulation. Many of these processes are associated with AKT1
						Sample collection: Department of Psychiatry, University Medical Center, Utrecht, The Netherlands / Parnassia PsychoMedical Center, The Netherlands / Center for Neuropsychiatric Schizophrenia Research, Psychiatric Center Glostrup, Denmark
						Consent / Ethics: The study was approved by Medical Research Ethics Committee (METC) of the University Medical Center Utrecht, The Netherlands and the Committees on Biomedical Research Ethics for the Capital Region of Denmark. All participants gave written informed consent
						SZ: Psychiatric diagnoses of SZ were made according to DSM-IV-TR criteria by trained clinicians using Standardized Psychiatric interviews either The Comprehensive Assessment of Symptoms and History (CASH) or the Composite international diagnostic interview (CIDI)
						HC: Unaffected controls
						Original study: de Jong <i>et al.</i> , PLoS ONE, 2012 (PMID: 22761806)
						Objective: To identify SZ-associated gene co-expression modules in the whole blood of SZ compared to HC
						Methods: Genome-wide expression profiling from whole blood of 106 SZ and 96 HC. SZ-associated gene co-expression modules
						Main results: Identification of 12 large gene co-expression modules associated with SZ. Two of the SZ-associated modules were replicated in an independent second dataset involving antipsychotic-free SZ and HC. One of these SZ-associated modules is significantly enriched with brain-expressed genes and with genetic risk variants for SZ, the hub gene in this module (ABCF1) is located in and regulated by the MHC-complex
GSE38484	Blood	Whole blood	HumanHT-12 V3.0	106	96	

GEO Accession Number	Tissue	Region / Cell Type	Microarray	SZ	HC	Description of the original study
GSE62333	Skin	Fibroblasts	HuGene-1_1-st	20	20	<p>Sample collection: Samples from Brescia and Verona, Italy</p> <p>Consent / Ethics: The project was approved by the local ethics committee. Written informed consent was obtained from the patients and controls. In the case of patients with a compromised ability to provide authorization, informed consent was signed by the legally authorized representative</p> <p>SZ: All SZ satisfied the DSM-IV criteria for SZ. Diagnoses were confirmed using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) diagnostic scale</p> <p>HC: Unrelated healthy volunteers were screened for DSM-IV Axis I disorders by expert psychologists using the Mini-International Neuropsychiatric Interview (M.I.N.I.). Only healthy volunteers without a history of drug or alcohol abuse or dependence and without a personal or first-degree family history of psychiatric disorders were enrolled in the study</p> <p>Exclusion criteria: For SZ and HC, exclusion criteria were defined as follows: mental retardation or cognitive disorder; serious somatic illnesses; uncorrected hypothyroidism or hyperthyroidism; age <18 and >70 years; metabolic disorders (diabetes); specific dermal diseases (e.g., dermal cancer or psoriasis). For HC, the presence of a history of drug, alcohol abuse or dependence, the presence of psychiatric disorders in first-degree relatives were additional exclusion criteria</p> <p>Original study: Caitane <i>et al.</i>, PLoS ONE, 2015 (PMID: 25668856)</p> <p>Objective: Differential expression analysis in skin fibroblasts of SZ and HC</p> <p>Methods: Genome-wide expression study comparing skin fibroblast transcriptomic profiles from 20 SZ and 20 HC</p> <p>Main results: Six genes (JUN, HIST2H2BE, FOSB, FOS, EGR1, TCF4) were strongly and significantly upregulated at the genome-wide level and confirmed by RT-PCR in SZ compared to HC</p>

Abbreviations: GEO, Gene Expression Omnibus; SZ, individuals with schizophrenia; HC, healthy controls; DLPFC, dorsolateral prefrontal cortex; PBMCs, peripheral blood mononuclear cells; BA, Brodmann Area

Supplementary Table 3. Genes with altered expression in the postmortem brain samples of individuals with schizophrenia compared with healthy controls

Gene	Cerebellum		Associative striatum		Hippocampus		Parietal cortex	
	Fold Change ¹	Adjusted p-value ²	Fold Change ¹	Adjusted p-value ²	Fold Change ¹	Adjusted p-value ²	Fold Change ¹	Adjusted p-value ²
<i>AIF1</i>	0.86	0.02	0.79	0.03	0.99	NS	0.90	NS
<i>CD68</i>	0.92	0.048	1.06	NS	1.11	NS	0.95	NS
<i>CSF1R</i>	0.90	0.025	0.89	NS	0.86	NS	0.91	NS
<i>CX3CR1</i>	0.92	NS	0.62	0.03	0.50	0.01	0.82	NS
<i>ITGAX</i>	0.94	0.03	0.95	NS	0.86	NS	0.92	NS
<i>IRF8</i>	0.85	0.03	0.92	NS	1.00	NS	0.91	NS
<i>OLR1</i>	0.90	NS	0.63	0.03	0.72	NS	0.74	0.01

Abbreviations: NS, not significant

¹Fold change represents the expression of the target gene in individuals with schizophrenia relative to that in healthy controls

²Significance of adjusted p-values set at 0.05

Supplementary Table 4. Results of ANCOVA and Bayesian analyses in the postmortem brain samples of individuals with schizophrenia compared with healthy controls

Gene	Cerebellum			Associative striatum			Hippocampus			Parietal cortex				
	ANCOVA			ANCOVA			ANCOVA			ANCOVA				
	F-statistic	p-value	BF ₁₀	Bayesian analyses	BF ₀₁	F-statistic	p-value	BF ₁₀	Bayesian analyses	BF ₀₁	F-statistic	p-value	BF ₁₀	Bayesian analyses
<i>AIF1</i>	9.94	0.002	20.76	0.05	0.37	0.37	NS	0.35	2.89	/	/	/	/	/
<i>CD68</i>	5.26	0.024	3.66	0.27	/	/	/	/	/	/	/	/	/	/
<i>CSF1R</i>	7.02	0.010	8.14	0.12	/	/	/	/	/	/	/	/	/	/
<i>CX3CR1</i>	/	/	/	/	7.47	0.011	0.172	5.80	0.172	5.99	0.021	138.73	0.007	/
<i>ITGAX</i>	6.18	0.015	3.57	0.28	/	/	/	/	/	/	/	/	/	/
<i>IRF8</i>	5.04	0.027	5.38	0.19	/	/	/	/	/	/	/	/	/	/
<i>OLR1</i>	/	/	/	/	7.49	0.010	12.37	0.08	0.08	/	/	16.89	<0.001	531.55

Abbreviations: BF₁₀, Bayes Factor quantifying the evidence in favor of H₁ compared with H₀; BF₀₁, Bayes Factor quantifying the evidence in favor of H₀ compared with H₁; NS, not significant

Supplementary Table 5. Genes with altered expression in the peripheral tissue samples of individuals with schizophrenia compared with healthy controls

Gene	Whole blood	
	Fold Change ¹	
	Adjusted p-value ²	
<i>AIF1</i>	1.14	0.004
<i>CD68</i>	0.87	0.002
<i>CSF1R</i>	0.85	0.002
<i>CX3CR1</i>	0.84	0.002
<i>ITGAX</i>	0.91	0.040
<i>IRF8</i>	1.12	0.004
<i>OLR1</i>	1.1	0.002
<i>TLR2</i>	1.1	0.002

¹Fold change represents the expression of the target gene in individuals with schizophrenia relative to that in healthy controls

²Significance of adjusted p-values set at 0.05

Supplementary Table 6. Results of ANCOVA and Bayesian analyses in the peripheral tissue samples of individuals with schizophrenia compared with healthy controls

Gene	Whole blood			
	ANCOVA	Bayesian analyses		
	F-statistic	p-value	BF ₁₀	BF ₀₁
<i>AIF1</i>	10.01	0.002	9.93	0.1
<i>CD68</i>	11.88	<0.001	43.84	0.02
<i>CSF1R</i>	22.48	<0.001	355.9	0.003
<i>CX3CR1</i>	37.42	<0.001	98837	0.00001
<i>ITGAX</i>	3.41	NS	1.33	0.76
<i>IRF8</i>	6.86	0.009	10.2	0.1
<i>OLR1</i>	15.19	<0.001	316.1	0.003
<i>TLR2</i>	16.43	<0.001	26.5	0.04

Abbreviations: BF₁₀, Bayes Factor quantifying the evidence in favor of H₁ compared with H₀; BF₀₁, Bayes Factor quantifying the evidence in favor of H₀ compared with H₁; NS, not significant

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