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# A la recherche d'un endophénotype de la schizophrénie : exploration des bases neuro-fonctionnelles du traitement des émotions

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**HAL Id: tel-04906583**

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Submitted on 22 Jan 2025

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THESE de DOCTORAT DE  
L'UNIVERSITE CLAUDE BERNARD LYON 1

École Doctorale N° 476  
Neurosciences et Cognition

Discipline : Neurosciences

Soutenue publiquement le 02/12/2024, par :  
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# A la recherche d'un endophénotype de la schizophrénie : exploration des bases neuro-fonctionnelles du traitement des émotions

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Ce travail a été soutenu par un prix de la Fondation Pierre Deniker en collaboration avec l'alliance Otsuka-Lundbeck, ainsi que par des financements du Centre Hospitalier Le Vinatier et du Centre Hospitalier-Universitaire de Saint-Etienne. Je remercie également la fondation Neurodis ainsi que l'Alliance Arqus pour avoir financé les mobilités scientifiques réalisées lors de ma thèse.

## Résumé

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### A la recherche d'un endophénotype de la schizophrénie : exploration des bases neuro-fonctionnelles du traitement des émotions

La schizophrénie est une maladie psychiatrique avec une forte composante génétique. Sur le plan comportemental, elle se caractérise par des altérations de la perception des émotions, qui jouent un rôle crucial dans le pronostic fonctionnel et l'étiopathogénie de la maladie. Des altérations similaires ont été observées chez les apparentés de patients, suggérant que le traitement des émotions pourrait constituer un endophénotype de la schizophrénie. En psychiatrie, les endophénotypes neurobiologiques suscitent un intérêt particulier : ils pourraient aider à surmonter la complexité des troubles polygéniques, améliorer la compréhension des mécanismes pathologiques, et permettre un dépistage plus précoce. Toutefois, il reste difficile de déterminer les corrélats cérébraux précis du traitement des émotions dans la schizophrénie. Cette thèse vise ainsi à explorer ces corrélats en tant que potentiel endophénotype de cette maladie.

Dans le **Chapitre I**, nous avons réalisé une méta-analyse d'études en imagerie par résonance magnétique fonctionnelle (IRMf). Nous avons montré qu'en comparaison avec des sujets contrôles, des individus à risque de développer une schizophrénie ne présentent pas d'anomalies d'activation cérébrale en réponse à des stimuli émotionnels, y compris dans des régions limbiques classiquement impliquées dans le traitement émotionnel comme l'amygdale. Puisque les émotions sont traitées par un ensemble de structures interconnectées, nous avons souligné l'importance d'examiner aussi la *connectivité* de ce réseau lors du traitement émotionnel.

Dans la continuité de ce travail, nous nous sommes intéressés à la littérature indiquant que, dans la schizophrénie, les stimuli neutres ne sont pas perçus comme tels, et que le traitement de ces stimuli est souvent accompagné par des *hyperactivations* du système limbique. Ainsi dans le **Chapitre II**, nous avons utilisé une approche méta-analytique pour étudier les réponses cérébrales aux stimuli neutres chez les apparentés des patients. A l'opposé des observations faites chez les patients, nous avons montré des *hypoactivations* limbiques chez les apparentés par rapport aux contrôles, ce qui pourrait suggérer la présence de facteurs protecteurs.

En nous appuyant sur ces travaux de méta-analyse, dans le **Chapitre III** nous avons réalisé une étude en IRMf pour examiner l'*activation* et la *connectivité* cérébrale en réponse à des stimuli émotionnels dans le continuum de la schizophrénie. Étant donné que les stimuli neutres sont perçus différemment par les patients, leurs apparentés et les contrôles, nous avons opté pour une *condition contrôle* plus appropriée. Nos résultats ont montré une absence de différences d'activation cérébrale dans la majeure partie du cerveau, dont l'amygdale, à la fois chez les apparentés et chez les patients atteints de schizophrénie, par rapport aux contrôles. De plus, nous avons observé une hypoactivation dans le cortex somatosensoriel chez les apparentés, qui semble aussi se manifester chez les patients. Au niveau de la connectivité cérébrale, nous avons trouvé que les apparentés présentent une connectivité accrue entre l'amygdale droite et le cuneus droit par rapport aux contrôles, ce qui renforce l'idée que l'activation cérébrale ne permet pas de saisir toutes les nuances du traitement émotionnel et suggère la présence d'un mécanisme compensatoire.

Pour aller plus loin, dans le **Chapitre IV**, nous avons examiné l'influence de certaines variations génétiques, qui sont susceptibles d'affecter les endophénotypes. Nous avons cartographié les anomalies d'*expression génétique de la microglie* à partir d'une base de données publique. Nous avons observé une réduction de l'expression de gènes associés à la microglie dans différentes régions cérébrales et au niveau périphérique, renforçant l'hypothèse d'une implication de la microglie dans la physiopathologie de la schizophrénie.

En **conclusion**, ce travail de thèse apporte des éléments clés à la compréhension des mécanismes cérébraux et génétiques de la schizophrénie, ainsi qu'à celle du traitement des émotions en tant qu'endophénotype potentiel de cette maladie.

**Mots clés :** schizophrénie, émotions, endophénotype, apparentés, neuroimagerie

## Abstract

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### Looking for an endophenotype of schizophrenia: an investigation into the neuro-functional bases of emotion processing

Schizophrenia is a disabling psychiatric disorder with a strong genetic component. Behaviorally, it is characterized by alterations in emotional perception, which play a crucial role in the functional prognosis and pathogenesis of the disease. Similar alterations have been observed in healthy first-degree relatives of patients with schizophrenia, suggesting that emotional processing could constitute an endophenotype of schizophrenia. In psychiatry, neurobiological endophenotypes are of particular interest: they may help overcome the complexity of polygenic disorders, improve our understanding of the pathological mechanisms of the disease, and possibly allow for earlier detection. However, it remains challenging to precisely determine the cerebral correlates of emotional processing in schizophrenia. In this context, this thesis aims to explore these cerebral correlates as a potential endophenotype of schizophrenia.

In **Chapter I**, using an image-based meta-analysis of functional magnetic resonance imaging (fMRI) studies, we showed that individuals considered at enhanced risk of schizophrenia do not exhibit abnormal brain activation in response to emotional stimuli compared with healthy controls. Since emotions are processed by a network of interconnected structures, we nonetheless highlighted the importance of also investigating the *connectivity* of this network during emotional processing.

Continuing from this initial work, we then examined the literature indicating that, in schizophrenia, neutral stimuli are not perceived as such, and that the processing of these stimuli is often accompanied by *hyperactivation* in the limbic system. Thus, in **Chapter II**, we used a meta-analytic approach to study brain responses to neutral stimuli in healthy relatives of patients. In contrast to observations made in patients, we showed limbic *hypoactivation* in relatives compared with healthy controls, suggesting the presence of protective factors.

Building on these meta-analytical works, in **Chapter III** we conducted an fMRI study to investigate brain *activation* and *connectivity* in response to emotional stimuli across the schizophrenia continuum. Given that neutral stimuli are perceived differently by patients,

their relatives, and healthy controls, we opted for a more appropriate *control condition*. Our results showed no differences in brain activation in response to negative stimuli across most of the brain, including in limbic regions such as the amygdala, in both relatives and patients with schizophrenia compared with healthy controls. Additionally, we observed hypoactivations in the somatosensory cortex in relatives, which also seem to manifest in patients. In terms of brain connectivity, we found that relatives exhibited increased connectivity between the right amygdala and the right cuneus compared with healthy controls, which reinforces the idea that brain activation does not capture all the nuances of emotional processing and suggests the presence of a possible compensatory mechanism.

To further our exploration, in **Chapter IV**, we examined the influence of certain genetic variations that might impact endophenotypes and the pathophysiology of schizophrenia. Specifically, we mapped *gene expression* anomalies associated with *microglia*, using a public database. We observed reduced expression of microglia-related genes in several brain regions as well as in peripheral blood, reinforcing the role of microglia in the pathophysiology of schizophrenia.

In **conclusion**, this thesis provides key contributions to the understanding of the cerebral and genetic mechanisms of schizophrenia, as well as to the role of emotional processing as a potential endophenotype of the disorder.

**Keywords:** schizophrenia, emotions, endophenotype, first-degree relatives, neuroimaging

## Remerciements

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Je remercie les rapporteurs de cette thèse, le Pr. Chantal Henry et le Pr. Stefan Kaiser, pour avoir accepté de relire ce manuscrit et d'apporter leur expertise. J'adresse également mes remerciements au Pr. Caroline Demily et au Dr. Pauline Favre pour leur rôle en tant qu'examinatrices de cette thèse.

Je tiens aussi à remercier le Pr. Gabriel Robert et le Dr. Jérôme Prado d'avoir suivi l'évolution de cette thèse lors des Comités de Suivi Individuel Doctoral, en y apportant leurs conseils et leur bienveillance.

Je remercie mes directeurs de thèse, le Pr. Eric Fakra et le Dr. Guillaume Sescousse, pour m'avoir accompagnée et soutenue depuis mes premiers pas dans le monde de la recherche et des neurosciences. Merci pour nos échanges scientifiques, qui ont été parmi les aspects les plus stimulants de ma thèse. Merci d'avoir toujours été présents, tant pour me soutenir lors des défaites que pour fêter nos succès. Merci Eric, de m'avoir confié le grand projet de recherche qu'est SchizEmo, et d'avoir apporté ton regard de clinicien ainsi que ton impressionnante expertise sur la schizophrénie et le traitement émotionnel. Merci Guillaume, pour tout le temps que tu as consacré à me former, notamment en neuroimagerie, pour avoir toujours trouvé un moment pour répondre à mes questions et encourager ma démarche scientifique, et plus généralement pour ta grande humanité. Tout simplement, merci à vous deux pour votre complémentarité ; vous rencontrer a probablement été l'une des meilleures chances de ma carrière étudiante et professionnelle.

Merci à l'équipe PsyR2 de m'avoir accueillie et de m'avoir apporté autant tout le long de mon doctorat. Ça a été un plaisir de partager le bureau des doctorantes avec Mélanie, partenaire d'un dîner presque parfait, Laure, qui a su illuminer le bureau avec son rire fou, et Mathilde, dont les hoquets me manquent déjà. Merci également aux doctorantes du bureau d'à côté, en particulier Ondine, pour le mélange de calme et de « zinzin » et Laetitia, pour la bonne humeur constante et la « tchatch ». Que ce soit lors des repas ou autour des apéros, vous avez contribué à créer une atmosphère chaleureuse et détendue. Merci à ceux qui sont arrivés plus tard ou qui sont passés par là, et à qui je souhaite le meilleur pour la suite : Anastasios, Nadine, Valentin, Gabriel, Thomas, Ilona et Maylis. Un grand merci à Jérôme, Marine, Jacquie, Cécilia et William pour leur esprit scientifique et pour avoir créé un environnement de travail si apaisant et convivial, que j'espère retrouver dans la suite de mon parcours professionnel. Enfin, merci à Leslie, pour faire vivre l'équipe avec son énergie et son enthousiasme, à Delphine pour ses conseils et ses soins infirmiers, pas seulement professionnels, et à Imelda pour son implication et sa franchise.



Merci aux participants, sans lesquels l'étude en imagerie par résonance magnétique n'aurait pas pu être réalisée. Et surtout un grand merci à toute l'équipe du Centre Hospitalier Universitaire de Saint-Etienne, Nadège, Lugdivine, Anabel, Lucie, Fouad pour leur implication totale et le rôle de premier plan dans le recrutement des participants.

Merci au Dr. Romain Rey de m'avoir impliquée dans un nouveau projet de recherche enthousiasmant et de m'avoir permis d'acquérir de nouvelles compétences.

Merci au Dr. El Chérif Ibrahim de m'avoir accueillie dans son laboratoire à Marseille et de m'avoir accompagnée tout au long des extractions génétiques, en prenant le temps de répondre à mes nombreux questionnements.

Merci à Franck Lamberton, non seulement pour les conseils méthodologiques, mais aussi pour m'avoir redonné confiance dans les échanges scientifiques.

Merci à mes amis et à ma famille de m'avoir accompagnée tout au long de ce parcours scientifique. Merci à ma mère et à mon père de m'avoir toujours donné la liberté de choisir ce que je voulais devenir, de m'avoir encouragée à donner le meilleur de moi-même et à me mettre à l'épreuve. Merci à ma mère pour les matchs de ping-pong entre deux paragraphes de ma thèse, et pour la belle combinaison de légèreté et de maturité avec laquelle tu vis la vie, que j'espère un jour atteindre. Et merci à Sara, comme tu l'as dit, tout simplement pour le fait d'être ma sœur et pour tout ce que cela implique : savoir que je pourrai toujours compter sur toi et me sentir libre d'être moi-même.

Merci à mes amies de toujours, Fra, Giulia et Elisa, avec qui, même lorsque tout change, rien ne change vraiment. Un grand merci également à Brizia, car au fil des années, tu es devenue une amie de toujours.

Merci à mes amis lyonnais (ou ex-lyonnais) qui ont rendu ces années si apaisantes et enrichissantes : à Erwan, le voisin idéal que tout le monde rêverait d'avoir, à Mariona, une colocataire en or, à Maya, ma petite fenêtre sur l'Italie en France et pilier solide dans ma vie, à Julie, partenaire de papotages et d'apéros, et à Carol, nouvelle venue à Lyon, mais avec qui le courant est immédiatement passé. Une mention spéciale à mes amis Marseillais, qui m'ont fait me sentir comme chez moi durant une période aussi courte qu'un séjour de deux mois : à Rosa, Damiano, Sal, Alberto, Sina et Perrine.

Enfin, bien sûr, merci à Tommy d'être là au quotidien, de me permettre de rire jusqu'aux larmes, et de m'apprendre à aborder les défis de la vie avec plus de légèreté. Tout simplement, merci d'être la personne avec qui j'ai envie de partager la suite.

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## Abréviations

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|                         |   |
|-------------------------|---|
| <i>5-HT<sub>2</sub></i> | 5-hydroxytryptamine                                     |
| <i>ADN</i>              | Acide Désoxyribonucléique                               |
| <i>ANOVA</i>            | Analyse de la Variance                                  |
| <i>APS</i>              | Attenuated Psychotic Symptoms                           |
| <i>ARMS</i>             | At Risk Mental States                                   |
| <i>ARN</i>              | Acide Ribonucléique                                     |
| <i>BIS</i>              | Balanced Integration Score                              |
| <i>BLIPS</i>            | Brief Limited Intermittent Psychotic Symptoms           |
| <i>CHR</i>              | Clinical High Risk                                      |
| <i>CIM</i>              | Classification Internationale des Maladies              |
| <i>CNV</i>              | Copy Number Variation                                   |
| <i>DSM</i>              | Manuel Diagnostique et Statistique des Troubles Mentaux |
| <i>eQTL</i>             | Expression Quantitative Trait Loci                      |
| <i>GRD</i>              | Genetic Risk and Deterioration Syndrome                 |
| <i>GWAS</i>             | Genome-Wide Association Studies                         |
| <i>IRMf</i>             | Imagerie par Résonance Magnétique Fonctionnelle         |
| <i>OHBM</i>             | Organization for Human Brain Mapping                    |
| <i>RDoC</i>             | Research Domain Criteria                                |
| <i>SNP</i>              | Single Nucleotide Polymorphism                          |
| <i>UHR</i>              | Ultra High Risk   |
| <i>VAAT</i>             | Variable Attention and congruency Task                  |

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## INTRODUCTION

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### La schizophrénie

#### *Épidémiologie et symptomatologie de la schizophrénie*

La schizophrénie est une maladie mentale qui touche environ 0.7 % de la population (Moreno-Küstner et al., 2018), soit 600.000 personnes en France. Elle touche légèrement plus souvent les hommes par rapport aux femmes, avec un ratio de 1.4 :1 (McGrath et al., 2008).

La schizophrénie se caractérise par **plusieurs types de symptômes** qui sont généralement regroupés en trois catégories principales : 1- les symptômes « positifs », qui viennent se rajouter au fonctionnement considéré normal, tel que les hallucinations, les idées délirantes ou les idées paranoïaques ; 2- les symptômes « négatifs », qui sont considérés comme une diminution dans les capacités dites normales, tels que l'émoussement affectif, l'apathie, ou le retrait social ; 3- les symptômes de « désorganisation » de la pensée, du langage et du comportement, qui se manifestent par exemple par des troubles du cours de la pensée ou un discours incohérent.

Le plus souvent c'est à cause des symptômes positifs que les patients décident de consulter un clinicien. Cependant, les symptômes négatifs -qui concernent plus que un patient sur deux (Bobes et al., 2009)- ainsi que cognitifs, sont les symptômes qui contribuent le plus au fardeau à long terme de la schizophrénie, étant fortement liés au pronostic fonctionnel (Carbon & Correll, 2014).

Historiquement, la conception de la schizophrénie repose sur les travaux pionniers d'Emil Kraepelin et d'Eugen Bleuler (Jablensky, 2010). Le psychiatre allemand Emil Kraepelin a introduit le terme « *dementia praecox* », considérant la schizophrénie comme une maladie dégénérative caractérisée par une détérioration cognitive progressive et irréversible, tout en mettant l'accent sur une approche biologique avec une vision biomédicale (Kraepelin, 1919). Par la suite, c'est le psychiatre suisse Eugen Bleuler qui a proposé le terme « schizophrénie », signifiant un « esprit divisé ». Il a souligné l'importance des facteurs psychologiques et environnementaux, suggérant que la schizophrénie pourrait être partiellement réversible. De plus, Bleuler a proposé d'utiliser le terme « schizophrénies » au pluriel, car cette maladie

mentale ne doit pas être considérée comme une entité unique, mais plutôt comme un ensemble de formes diverses (Bleuler, 1911).

Actuellement, les systèmes de classification utilisés pour diagnostiquer et classer les troubles psychiatriques se basent en partie sur ces travaux pionniers. Parmi ces systèmes, les plus utilisés sont le *Manuel diagnostique et statistique des troubles mentaux* (DSM) et la *Classification internationale des maladies* (CIM), qui définissent des critères diagnostiques précis afin de permettre une identification standardisée des troubles psychiatriques.

En France, dans la pratique clinique comme dans la recherche, le DSM est le manuel le plus utilisé. La version actuelle, publiée en 2013, est la cinquième édition (**DSM-5**). Selon les critères du DSM-5, un diagnostic de schizophrénie est posé lorsqu'une personne présente pendant au moins un mois deux symptômes ou plus parmi ces cinq domaines (critère A) : hallucinations, idées délirantes, discours désorganisé, comportement désorganisé ou catatonique, symptômes négatifs. Au moins un des deux symptômes doit être parmi les trois premiers listés ci-dessus. Ensuite, un deuxième critère (B) postule que l'un ou plusieurs domaines majeurs du fonctionnement (tel que le travail, les relations interpersonnelles ou les soins personnels) soient atteints, en soulignant la nécessité que le symptôme soit associé à une incapacité afin d'être considéré comme pathologique. D'autres critères complètent le diagnostic de ce trouble. Le trouble doit persister depuis au moins six mois (critère C), incluant des phases prodromiques ou résiduelles. D'autres troubles, comme le trouble schizo-affectif, dépressif ou bipolaire, doivent être exclus (critère D). Il est également souligné que la cause ne doit pas être liée à une substance ou à une autre pathologie médicale (critère E). Enfin, si des antécédents de trouble du spectre de l'autisme ou de trouble de la communication existent, le diagnostic de schizophrénie n'est posé que si des symptômes délirants ou hallucinatoires significatifs sont présents (critère F).

Dans les dernières années, plusieurs limites de ces systèmes de classification sont en train d'émerger. En effet, ces systèmes se basent exclusivement sur les symptômes pour classer les troubles mentaux, ce qui entraîne une grande hétérogénéité, des comorbidités fréquentes, et une absence de conceptualisation dimensionnelle, rendant difficile une compréhension nuancée des troubles mentaux.

Une nouvelle approche de recherche sur les maladies mentales, appelée **Research Domain Criteria (RDoC)**, a été développée pour répondre aux limites des systèmes de diagnostic traditionnels. Conçu par le *National Institute of Mental Health* (NIMH), l'agence fédérale des États-Unis dédiée à la recherche sur les troubles mentaux, ce cadre émerge de la nécessité d'adopter une approche plus scientifique et biologique. L'objectif est d'améliorer la compréhension et le traitement des maladies mentales en se concentrant sur les mécanismes sous-jacents, souvent transdiagnostiques, qui intègrent les aspects génétiques, neurobiologiques, et cognitifs, plutôt que sur de simples regroupements de symptômes. Le projet RDoC ne visent pas à remplacer le DSM dans la pratique clinique, mais plutôt à offrir un cadre de recherche mieux adapté à l'hétérogénéité clinique observée.

## *Impact de la schizophrénie*

La schizophrénie a un impact majeur sur la personne atteinte ainsi que sur son entourage.

En effet, elle fait partie des **dix premières causes d'incapacité dans le monde** (Vos et al., 2017). Ainsi, la qualité de vie des personnes vivant avec une schizophrénie est fortement impactée, avec des taux de chômage atteignant 87 % en France (Bebbington et al., 2005).

De plus, selon une méta-analyse de Saha et collaborateurs (2007), la schizophrénie entraîne une diminution de 15 à 20 ans de l'espérance de vie. Non seulement le suicide est associé à un plus haut ratio de mortalité par rapport à la population générale -avec environ 4 % de personnes vivant avec une schizophrénie décédant par suicide (par rapport à 1.2 % dans la population générale) (Tanskanen et al., 2018), mais la majorité des catégories de causes de mort étudiée dans cette méta-analyse sont plus élevée chez les personnes atteintes de schizophrénie (Saha et al 2007).

Par ailleurs, la pathologie a aussi des **conséquences néfastes sur l'entourage des patients**. Les aidants des patients considèrent que l'accompagnement du patient constitue une charge importante (Rahmani et al., 2022) et leur qualité de vie perçue est faible (Leng et al., 2019). Chez les aidants des patients, on observe une diminution du travail ainsi qu'une augmentation de symptômes anxieux et dépressifs (Njah et al., 2023).

Enfin, la schizophrénie a également un **impact sociétal important**. En particulier, l'impact économique de la schizophrénie est considéré comme majeur. Le coût de la maladie est estimé à environ 1.1 % des dépenses nationales de santé d'un pays, et les soins hospitaliers constituent la dépense principale (Charrier et al., 2013). Même pour les patients non hospitalisés, les coûts sont considérés très élevés et, en proportion, dépassent même ceux liés à la dépression (Desai et al., 2013).



## *Le continuum de la schizophrénie et son déclenchement*

La schizophrénie est une maladie qui se déclenche généralement à la fin de l'adolescence, avec un pic d'apparition qui a été décrit chez les hommes au début ou au milieu de la vingtaine, et chez les femmes plus tardivement à la fin de la vingtaine (Giordano et al., 2021). Bien que plus rares, des déclenchements précoces (avant 18 ans) ou très précoces (avant 13 ans) peuvent survenir, tout comme des déclenchements tardifs (après 40 ans) ou très tardifs (après 60 ans), ces derniers étant beaucoup plus fréquents chez les femmes (Chen et al., 2018).

Même si les manuels de classification des troubles psychiatriques se basent sur une vision dichotomique de la maladie, supposant qu'il existe une discontinuité claire entre « sain » et « pathologique », une approche dimensionnelle, considérant la schizophrénie comme s'établissant sur un « continuum » entre personne saine et personne atteinte, est de plus en plus considéré.

Dans la littérature par exemple, des études montrent que des symptômes psychotiques subcliniques peuvent être retrouvés également dans la population générale, avec une prévalence qui atteint le 8.4 % pour les délires de persécution (Nuevo et al., 2012).

Plusieurs étapes ont été décrites dans le continuum de la schizophrénie (Fusar-Poli et al., 2013). Tout d'abord, on peut parler d'une phase dite « **premorbide** », qui décrit le niveau du fonctionnement d'un individu de sa naissance au déclenchement des premiers symptômes atténués. Dans cette phase des dysfonctionnements cognitifs, moteurs et/ou sociaux subtils peuvent déjà se manifester. Ces signes incluent des traits de personnalité dits « schizotypiques », qui peuvent être identifiés à travers une approche psychométrique basée sur des questionnaires (Cicero et al., 2014). Les taux de conversion vers la schizophrénie des individus avec des traits schizotypiques élevés n'ont pas encore été déterminés, mais une étude de suivi de 10 ans a trouvé un taux de transition vers la psychose d'environ 5 % (Chapman et al., 1994), et une revue longitudinale a souligné une association entre les traits schizotypiques et la conversion à la psychose (Debbané et al., 2015).

Ensuite, on peut parler d'une phase dite « **prodromique** ». Cette phase est décrite comme une période de changement fonctionnel qui précède le déclenchement de la maladie et qui durerait en moyenne entre 1 et 5 ans (Conroy et al., 2018). Depuis l'introduction de ce concept

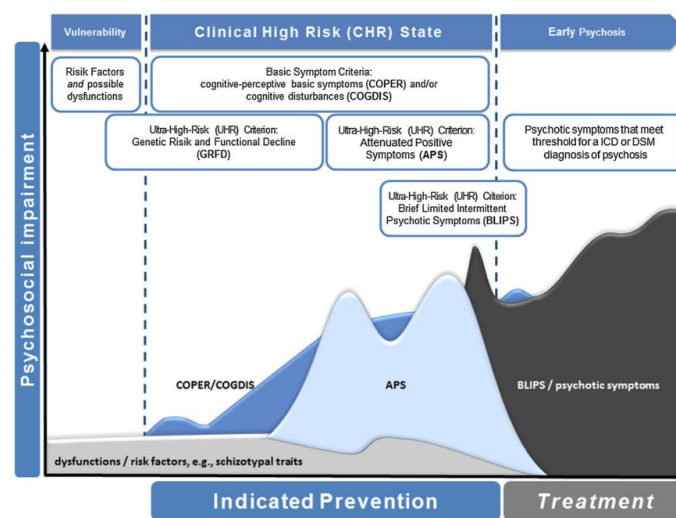
dans les années 1990 (Yung et al., 1996), un large courant prône l'importance de cette phase pour la détection précoce de la maladie et l'identification des biomarqueurs (Yung & McGorry, 1996). En effet, une méta-analyse a estimé que pour la majorité des patients (78 %) l'entrée dans la maladie serait précédée par cette phase (Benrimoh et al., 2024). Dans la littérature, plusieurs définitions ont été employées afin d'identifier des sujets dans cette phase, et elle a été décrite avec les termes de « *clinical high risk* » (CHR), « *ultra high risk* » (UHR) ou « *at risk mental states* » (ARMS). Comme résumé par Fusar-Poli et collaborateurs, la présence d'un risque clinique élevé pour le développement de la schizophrénie est déterminée par l'un des trois critères suivants : 1- des symptômes psychotiques atténués, « *Attenuated Psychotic Symptoms* » (APS), c'est-à-dire des symptômes positifs sous le seuil diagnostique ou un contenu de la pensée inhabituel ; 2- des épisodes psychotiques brefs, limités et intermittents, « *Brief Limited Intermittent Psychotic Symptoms* » (BLIPS), c'est-à-dire des symptômes psychotiques avec une durée limitée dans le temps ; et 3- un trait de vulnérabilité combiné à une diminution marquée du fonctionnement psychosocial, connu sous le nom de « *genetic risk and deterioration syndrome* » (GRD) (Fusar-Poli et al., 2013). Il a été estimé que 22 % des individus avec un risque clinique évoluent vers la schizophrénie après un an, et ce taux peut augmenter jusqu'à 36 % après 3 ans (Fusar-Poli et al., 2012).

Dans une révision du modèle proposée par Fusar-Poli (2017), le risque génétique est ré-évalué comme faisant partie de la phase premorbide, et le risque clinique est divisé en trois stages avec un risque de transition de plus en plus élevés : les personnes présentant des symptômes négatifs ou cognitifs, les personnes avec des symptômes psychotiques atténués (APS), et les personnes avec des épisodes psychotiques brefs, limités et intermittents (BLIPS).

Depuis les dernières années, de nombreux travaux se sont focalisés sur ces populations à risque clinique. La distinction entre population à risque et prodrome est capitale. La phase prodromique est un concept essentiellement rétrospectif, car un prodrome n'existe qu'une fois que la maladie s'est manifestée, alors que la grande majorité des personnes à haut risque clinique ne développent pas la schizophrénie (Addington et al., 2020). Une autre limite de cette approche est qu'elle se base souvent sur des individus dits « en recherche d'aide » (*help-seeking*), ce qui pourrait restreindre les recherches scientifiques à cette catégorie spécifique de population, au détriment des individus à risque qui ne sollicitent pas d'aide. De plus, 73 %

de ces individus présentent une comorbidité avec un diagnostic de l'axe I, comme un trouble dépressif ou anxieux (Fusar-Poli et al., 2014).

Enfin, dans le continuum psychotique les personnes vivant un **premier épisode psychotique** sont considérées comme le plus à risque de développer une schizophrénie chronique, avec un taux de transition dans les cinq ans suivant l'épisode psychotique d'environ 87 % (Inchausti et al., 2023). Toutefois, il y a plus d'ambiguïté sur la définition opérationnelle précise de cette population (Breitborde et al., 2009). Pour une illustration du continuum de la schizophrénie, se référer à la Figure 1.



**Figure 1**

*Le continuum psychotique, tirée de Schultze-Lutter et al., 2015 et adaptée de Fusar-Poli et al., 2013. Cette figure montre l'évolution des symptômes à travers différentes phases. Au stade prémorbide, on retrouve d'éventuelles altérations fonctionnelles ainsi que la présence de traits schizotypiques. La phase suivante, celle prodromique avec un haut risque clinique (CHR), se caractérise par des « symptômes de base », tels que les symptômes fondamentaux cognitifs-perceptifs (COPER), qui englobent des altérations dans la perception de la réalité, ainsi que les perturbations cognitives (COGDIS), qui incluent des difficultés dans les fonctions cognitives. D'autres critères comprennent un risque génétique associé à un déclin fonctionnel (GDR), des symptômes positifs atténués (APS) et des épisodes psychotiques intermittents brefs (BLIPS). Enfin, la transition vers la psychose marque la phase finale, où les symptômes psychotiques, auparavant brefs, limités et intermittents, deviennent persistants et durables.*

## *La composante génétique dans la schizophrénie*

La schizophrénie a une héritabilité génétique qui est considérée comme élevée. En effet, les études chez des jumeaux montrent une concordance qui varie entre 33 % pour les jumeaux monozygotes et 7 % pour les jumeaux dizygotes (Hilker et al., 2018). L'héritabilité génétique - qui compare les taux de concordance des traits entre ces deux types de jumeaux afin de faire la part entre la composante génétique et celle environnementale- a été estimée à 79 % (Hilker et al., 2018), pouvant ainsi expliquer une partie importante du risque de développer la maladie.

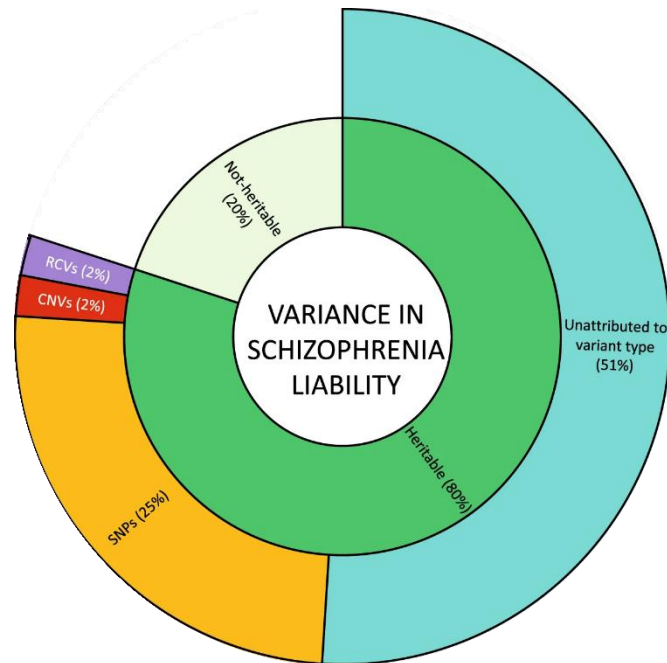
Toutefois, la schizophrénie est considérée comme un **trouble polygénique complexe**. En effet, des milliers de variantes génétiques communes avec de faibles effets ainsi que des variantes génétiques rares avec des tailles d'effets plus larges, mais présentes seulement dans un sous-groupe de patients, contribuent à l'architecture polygénique de la schizophrénie (Smeland et al., 2020).

A ce jour, les études d'association pangénomique (« *genome-wide association studies* » ou **GWAS**), ont permis d'apporter des nouvelles pistes dans la compréhension des bases génétiques de la schizophrénie et de ces processus sous-jacents. Ces études, qui s'intéressent à l'entièreté du génome, nécessitent d'un nombre très élevé de participants afin d'obtenir une puissance statistique satisfaisante et éviter les faux positifs (Farrell et al., 2015). Dans l'objectif de réunir des gros échantillons, des consortiums tel que le *Psychiatric Genomics Consortium* ont donc été créés, recherchant des polymorphismes nucléotidiques (« *single nucleotide polymorphisms* », SNPs). L'une des premières études conduites par ce consortium a permis d'identifier 128 associations indépendantes avec des polymorphismes nucléotidiques à travers 108 régions chromosomiques (ou loci) (Ripke et al., 2014). Depuis, la taille des échantillons dans ces études GWAS n'a cessé d'augmenter. La dernière étude du consortium, publié en 2022, a inclus plus de 76 000 patients vivant avec une schizophrénie et 243 000 sujets contrôles (c'est-à-dire des volontaires sans troubles psychiatriques). Cette étude a mis en évidence **342 polymorphismes génétiques** dans 287 loci (Trubetskoy et al., 2022). A ce jour, la plus grande association concerne le **complexe majeur d'histocompatibilité** du chromosome 6, un locus qui code essentiellement pour des gènes impliqués dans la fonction immunitaire (Ripke et al., 2014 ; Trubetskoy et al., 2022). Ces études ont donc porté à la

découverte d'un nombre très important de variations génétique liées aux polymorphismes nucléotidiques, qui ne sont pas considérées comme rares (vu qu'elles affectent plus que 1 % de la population générale), mais qui sont associées à un risque très faible (avec des tailles d'effets réduites), chacune n'expliquant qu'une petite partie de la prédisposition génétique à la maladie. A côté de ces variations génétiques, dans la schizophrénie il peut également y avoir des changements structurels dans les séquences de l'acide désoxyribonucléique (ADN), dans lesquels une section plus large de l'ADN, qui habituellement contient plusieurs gènes, peut être dupliquée ou supprimée -connus sous le nom de « *Copy Number Variation* » (CNV). Le premier CNV associé à la schizophrénie a été le syndrome de délétion 22q11.2 (Murphy et al., 1999), qui porte à un diagnostic de schizophrénie dans environ 20 % des cas (Bassett et al., 2005). Ces variations sont considérées comme rares (vu qu'elles touchent moins de 1 % de la population générale) et sont associées à des tailles d'effet plus importantes concernant le risque de développer une schizophrénie (Marshall et al., 2017). Actuellement, **12 CNVs** ont été identifiées comme facteurs de risque de la schizophrénie, mais individuellement elles ne sont présentes que dans 0.015 % - 0.64 % des cas (Owen et al., 2023).

Même si les résultats des GWAS ont montré leur solidité et réplicabilité (à titre d'exemple, dans le travail de Trubetskoy et collaborateurs (2022), tous les 128 polymorphismes nucléotidiques identifiés dans l'étude de 2014 (Ripke et al., 2014), à l'exception d'un, ont été répliqués), nous sommes encore loin d'avoir une compréhension complète de la composante génétique de la schizophrénie. En effet, ces variations génétiques expliquent environ 30 % de la variance totale -incluant à la fois les facteurs environnementaux et génétiques- de la susceptibilité à la schizophrénie, ce qui correspond à environ 40 % de l'héritabilité génétique (Owen et al., 2023), alors que, pour rappel, ce taux est estimé à environ 80 % dans les études sur les jumeaux (Hilker et al., 2018). A ce jour, il reste difficile de comprendre les raisons de **l'écart entre l'héritabilité expliquée par les données génomiques actuelles et celle attendue selon les études sur les jumeaux**. Tout d'abord, les limites des technologies actuellement disponibles pour conduire les études GWAS ont été mises en avant. Ensuite, l'estimation de 40 % d'héritabilité des études GWAS pourrait avoir été sous-évaluée, par exemple à cause de l'hétérogénéité des participants inclus, tandis que l'estimation d'héritabilité des études de jumeaux de 80 % pourrait avoir été surestimée, par exemple en raison d'un contrôle insuffisant de l'environnement partagé dans les études sur les jumeaux (Owen et al., 2023).

En effet, certains facteurs de risque environnementaux sont partagés au sein d'une même famille (comme l'urbanisation ou le milieu socio-économique défavorable), et leur impact pourrait ainsi avoir été confondu avec celui de la génétique (voir la Figure 2 pour un résumé de notre compréhension actuelle des influences génétiques sur la schizophrénie).



**Figure 2**

*Différentes contributions à la variance de la susceptibilité à la schizophrénie (adaptée de Owen et al., 2023). L'anneau intérieur reflète une héritabilité génétique estimée à environ 80 % à partir d'études sur les jumeaux, le reste étant attribué à des facteurs non héréditaires (comme les facteurs environnementaux). L'anneau extérieur montre la contribution des différents variants génétiques à cette héritabilité. 51 % de la variance totale reste non attribuée à des types de variants connus. Abréviations : RCV, rare coding variants ; CNV, copy number variants ; SNP, single nucleotide polymorphisms.*

Bien que les études sur les SNPs et les CNVs aient permis d'identifier des variants génétiques associées à la schizophrénie, elles ne fournissent pas d'informations directes sur la manière dont ces variants affectent la fonction des gènes. De plus, d'autres phénomènes, souvent influencés par des facteurs environnementaux, tels que les mécanismes épigénétiques (comme la méthylation de l'ADN), interviennent sans altérer la séquence d'ADN et ne peuvent

pas être détectés par une simple analyse génétique. Dans ce contexte, un intérêt particulier est porté à l'étude du transcriptome, c'est-à-dire tous les types d'acide ribonucléique (ARN) qui sont transcrits à partir de l'ADN. En effet, le génome humain est constitué d'ADN, qui est organisé en 20 000 - 25 000 gènes. Presque toutes les cellules humaines contiennent les mêmes gènes, mais ce qui différencie les cellules et les tissus est la façon dont elles expriment ces gènes. Ainsi, les études sur les ARN messagers (ARNm) peuvent révéler comment l'expression des gènes varie entre les différents tissus ou même au sein de différentes régions du cerveau. Cette approche est particulièrement utile pour comprendre les mécanismes de la schizophrénie, car elle offre une perspective plus rapprochée sur la façon dont les gènes s'expriment et interagissent avec les facteurs environnementaux, permettant de mieux appréhender les variations des phénotypes (c'est-à-dire les traits observables d'un individu, y compris les caractéristiques comportementales et cognitives). L'étude de l'expression génétique permet ainsi de faire le lien entre l'information génétique contenue dans l'ADN et la production finale de protéines, en regardant plus loin dans la chaîne qui relie les gènes aux phénotypes.

Dans l'une des études postmortem de séquençage de l'ARN les plus larges, Fromer et collaborateurs ont utilisé des tissus du cortex préfrontal dorsolatéral d'environ 300 patients pour déterminer si l'expression génétique reflétait les loci identifiés par les études GWAS, en analysant les loci de caractères quantitatifs (ou eQTL pour « *expression quantitative trait loci* »), qui sont des loci génétiques associés à une altération de l'expression génétique (Fromer et al., 2016). Ils ont trouvé que les variations génétiques dans 20 de 108 loci identifiés à l'époque -donc environ 20 % des loci- alternent au moins l'expression d'un ou plusieurs gènes. En regardant les patterns de coexpression de ces gènes, il a été observé que ces gènes font partie des systèmes impliqués dans des processus de régulation des membranes post-synaptiques, dans la transmission synaptique et dans les canaux potassiques voltage-dépendants.

Une revue systématique récente des études « *transcriptome-wide* », analysant l'expression génétique ou les transcrits de tout le génome dans différents types de tissus cérébraux et périphériques, a mis en évidence une grande variabilité dans les résultats et la direction des

effets rapportés par les études. Cependant, les rares gènes les plus solidement rapportés étaient en lien avec la fonction immunitaire (Merikangas et al., 2022).

Enfin, une large étude transcriptomique incluant 700 échantillons du cortex cérébral provenant de sujets contrôles ainsi que d'individus atteints de troubles psychiatriques (tels que la schizophrénie, l'autisme, ou le trouble bipolaire) a montré qu'il existe au moins en partie un recoupement des patterns d'expression génétique dans ces différents troubles. La sévérité des altérations transcriptomiques semble être la plus prononcée dans l'autisme, comparable entre les patients atteints de schizophrénie et bipolaires, et moins marquée dans la dépression (Gandal et al., 2018).

Il faut noter qu'un intérêt particulier est porté vers l'**expression génétique des tissus périphériques**. En effet, il s'agit d'un outil prometteur pour explorer le transcriptome de manière peu invasive et permettre l'identification de biomarqueurs d'expression génétique susceptibles d'aider les cliniciens à prédire la pathologie de la schizophrénie. D'une part, la schizophrénie est considérée comme un trouble « à corps entier », dans le sens que certaines études montrent également des altérations en dehors du système nerveux central (Merikangas et al., 2022; Pillinger et al., 2019). D'autre part, le sang contient jusqu'à 80 % des gènes codés dans le génome humain, et ces tissus périphériques partagent de nombreux chemins biologiques et génétiques avec le système nerveux central. Ainsi, le sang peut également être un indicateur de l'expression génétique cérébrale. Dans ce sens, une étude a montré que 90 % des voies moléculaires hautement prédictives dans le cerveau en neurodégénérescence figurent également parmi les voies les plus pertinentes détectées dans les données sanguines (Iturria-Medina et al., 2020). Une méta-analyse des gènes dérégulés à la fois au niveau central et périphérique a mis en évidence l'inflammation comme le principal processus biologique associé à la schizophrénie, en soulignant le rôle potentiel de la microglie et des macrophages (Bergon et al., 2015).



## *Étiologie de la schizophrénie*

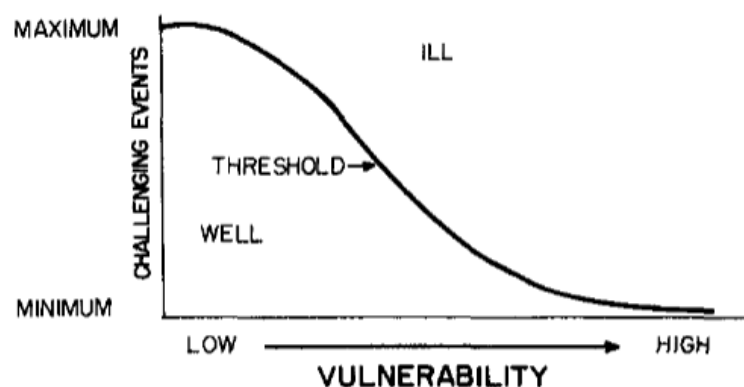
Les causes de la schizophrénie restent largement inconnues à ce jour. Cependant, les travaux pionniers de Weinberger (1987) et Murray et Lewis (1988) reconnaissent la schizophrénie comme un **trouble neurodéveloppemental**. Selon ces auteurs, des conditions génétiques et environnementales défavorables survenant précocement peuvent perturber le développement normal du cerveau et déclencher l'apparition des symptômes de la schizophrénie à l'adolescence. Contrairement aux troubles neurodégénératifs, dans lesquels la maladie dégrade un cerveau initialement sain, cette théorie suggère que la schizophrénie résulte d'une construction précoce anormale du cerveau. Toutefois, bien que la majorité des études soutiennent à ce jour une perspective neurodéveloppementale de la schizophrénie, ces mécanismes ne sont pas mutuellement exclusifs, et les deux formes peuvent coexister (Gupta & Kulhara, 2010).

Parmi les processus intervenants précocement et qui ont été étroitement liés à la maladie, on retrouve l'**inflammation**, c'est-à-dire l'ensemble des réactions du système immunitaire en réponse à des agents pathogènes. En effet, des études ont associé à un risque accru de schizophrénie les infections prénatales (Brown & Derkits, 2010), l'inflammation maternelle pendant la grossesse (Choudhury & Lennox, 2021), les complications obstétricales (Cannon et al., 2002), ainsi que les infections durant l'enfance (Khandaker et al., 2012). Ainsi, l'exposition à divers virus, comme le virus de la grippe ou le virus de l'herpès simplex, sont considérés comme des facteurs de risque de psychose (Kotsiri et al., 2023). De plus, l'observation d'une fréquence plus élevée de cas de schizophrénie pendant les mois d'hiver (Hsu et al., 2021), semble indiquer une exposition accrue des mères, pendant la grossesse, à des infections virales respiratoires durant des périodes cruciales du développement cérébral de leur enfant (Tochigi et al., 2004).

Nos connaissances actuelles montrent que le cerveau humain n'atteint généralement sa pleine maturité qu'à l'âge d'environ 25 ans (Arain et al., 2013). L'un des processus clés de cette maturation postnatale est l'**élagage synaptique**, un mécanisme par lequel certaines synapses sont supprimées de manière sélective, permettant ainsi l'élimination des structures plus faibles et le renforcement des synapses restantes, ce qui est essentiel pour la constitution d'un cerveau adaptatif (Johnson & Hyman, 2022). Une perturbation de ce processus pendant

l'adolescence, résultant dans un élagage excessif, a été proposée comme un facteur sous-jacent de troubles psychiatriques tels que la schizophrénie (Feinberg, 1982).

Notre compréhension actuelle de la schizophrénie est le mieux résumée par le **modèle de stress-vulnérabilité** initialement proposé par Zubin et Spring en 1977 (schématisé dans la Figure 3). Selon ce modèle, l'interaction de multiples facteurs génétiques entre eux ainsi qu'avec des facteurs de risque environnementaux entraînerait des anomalies neurodéveloppementales prédisposant au développement ultérieur de la maladie. Une fois cette vulnérabilité établie, l'apparition de la maladie et son évolution, y compris les rechutes, sont déterminées par l'interaction dynamique des facteurs biologiques et psychosociaux. Parmi les facteurs environnementaux jouant un rôle dans le développement de la schizophrénie, on retrouve la consommation de cannabis, les adversités de l'enfance, en particulier les traumatismes, l'environnement urbain et le statut d'immigrant (van Os et al., 2010). De manière plus large, ce que tous ces facteurs de risque ont en commun est une exposition accrue à du stress chronique. A titre d'exemple, le stress semble avoir un rôle de médiateur dans l'association entre l'urbanité et la schizophrénie (Heinz et al., 2013) et la consommation de cannabis a été associée à un stress accru (Glodosky et al., 2021). Toutefois, ce lien est probablement plus complexe, car d'autres facteurs peuvent également intervenir. Dans le cas de l'urbanité, il a été proposé que des éléments physiques comme l'exposition à la pollution de l'air et l'accès aux espaces verts pourraient aussi jouer un rôle (Pignon et al., 2023).



*Figure 3*

*Représentation graphique du modèle de stress-vulnérabilité, tirée de Zubin et Spring (1977). L'axe vertical indique l'intensité des événements stressants, et l'axe horizontal la vulnérabilité*

*individuelle. Lorsque la vulnérabilité est faible, un nombre élevé d'événements stressants est nécessaire pour franchir le seuil diagnostique. Inversement, à mesure que la vulnérabilité augmente, même un faible niveau de stress peut déclencher l'apparition de la maladie.*

Afin de décrire le rôle prédominant du stress, l'analogie du « seau de vulnérabilité au stress » est souvent utilisée (illustrée dans la Figure 4). La taille du « seau » représente la vulnérabilité de l'individu, essentiellement influencée par des facteurs génétiques, neurobiologiques ou développementaux. Le stress, sous l'action de facteurs environnementaux, contribue à remplir le seau. Lorsque le niveau de stress dans le seau dépasse la capacité de résilience individuelle, c'est-à-dire le seuil de tolérance, cela entraînerait le déclenchement du trouble, ainsi que l'apparition des symptômes.



**Figure 4**

*Schéma illustrant l'analogie du seau de vulnérabilité au stress (« Stress Vulnerability Bucket »). Chaque facteur (vie urbaine, traumatisme, consommation de cannabis, migration, etc.) contribue à remplir le « seau de stress ». Lorsque le niveau de stress dépasse la capacité d'adaptation individuelle, cela peut déclencher des troubles psychiatriques tels que la schizophrénie.*

## Traitement

Aujourd'hui la schizophrénie est principalement prise en charge pharmacologiquement, à travers l'utilisation de médicaments antipsychotiques. Ces médicaments ont été introduits dans les années cinquante et agissent essentiellement comme antagonistes aux **récepteurs post-synaptiques D2 de la dopamine**. Plus tard, les antipsychotiques de deuxième génération, dits « atypiques », ont fait leur apparition, avec une double action sur les récepteurs 5-hydroxytryptamine (5-HT<sub>2</sub>) de la sérotonine ainsi que les récepteurs dopaminergiques. Enfin les antipsychotiques de troisième génération se lient aux récepteurs D3 et sont des antagonistes partiels des récepteurs D2 (Allott et al., 2024). De façon générale, les antipsychotiques se sont montrés efficaces pour les symptômes positifs de la schizophrénie, tels que les hallucinations et les idées délirantes, qui semblent être liées à une signalisation dopaminergique excessive dans le striatum. Toutefois, les effets secondaires sont nombreux, tels que une prise de poids, des constipations, ou des troubles du mouvements (comme la dyskinésie tardive -des mouvements involontaires et répétitifs, l'akathisie -un besoin irrésistible de bouger, ou des tremblements, souvent comparés à ceux observés dans la maladie de Parkinson) (Stroup & Gray, 2018). A quelques exceptions près, les médicaments semblent peu efficaces pour les symptômes négatifs et les déficits cognitifs (Allott et al., 2024).

Environ un patient sur quatre qui vit un premier épisode psychotique montre une résistance au traitement (Siskind et al., 2022), définie comme la persistance de symptômes après deux essais médicamenteux ou plus, à une dose et une durée adéquate. De façon intéressante, il semblerait que les apparentés de premier ou deuxième degré des patients non-répondeurs au traitement ont plus de risque de développer la maladie que les apparentés des patients répondeurs, en suggérant que ces patients non répondeurs pourraient souffrir d'une forme plus « familiale » (Joober et al., 2005). De plus, la pathophysiologie des patients résistants au traitement pourrait être liée aux mécanismes glutamatergiques -avec une augmentation de glutamate notamment dans le cortex cingulaire antérieur- plutôt que dopaminergiques (Egerton et al., 2021). Au niveau médicamenteux, la clozapine semble souvent être le traitement le plus efficace pour les patients résistants (Raguraman et al., 2005). De plus, la **stimulation non-invasive** est souvent proposée à ces patients, avec des techniques telles que la stimulation magnétique transcrânienne ou la stimulation transcrânienne à courant continu,

qui ont pour objectif de restaurer l'activité cérébrale qui est perturbée dans certaines régions ou réseaux fonctionnels. Deux principales applications ont été suggérées : réduire l'hyperactivité de la jonction temporo-pariétale, liée aux hallucinations auditives ; et augmenter l'activité réduite du cortex préfrontal, en particulier du cortex préfrontal dorsolatéral gauche, associée aux symptômes négatifs (Brunelin et al., 2022). Ces applications ont montré une efficacité classée entre les catégories B (probable) et C (possible) (Brunelin et al., 2022).

Enfin, en ce qui concerne les interventions psychosociales, l'*American Psychiatric Association* recommande les **thérapies cognitivo-comportementales**, ainsi que la **psychoéducation**, soulignant également la nécessité de mettre en place des interventions familiales (Keepers et al., 2020). En effet, ces interventions ont montré des bénéfices significatifs dans la réduction du risque de rechute (Bighelli et al., 2021).

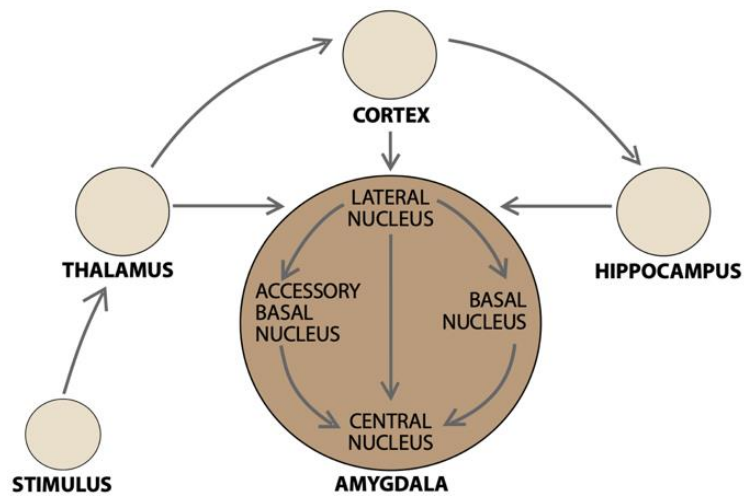
## Le traitement des émotions dans la schizophrénie

Selon le dictionnaire de l'*American Psychological Association*, une émotion est « une réaction complexe, impliquant des éléments expérientiels, comportementaux et physiologiques, par laquelle un individu tente de faire face à une situation ou à un événement personnellement significatif ».

Les émotions sont communément distinguées en émotions de base et émotions complexes. En ce qui concerne les émotions de base, les six communément reconnues sont celles identifiées par le psychologue Paul Ekman en 1999 : la joie, la tristesse, la peur, la colère, la surprise et le dégoût (Ekman, 1999). Les émotions complexes seraient une combinaison à différents niveaux de ces six émotions de base. Ces émotions de base sont universelles, et se retrouvent à travers les différentes cultures. En effet, selon la vision évolutionniste, ces émotions se sont développées et ont été sélectionnées en raison de leur valeur adaptative.

Sur le plan cérébral, plusieurs études se sont intéressées aux bases neurofonctionnelles du traitement émotionnel. Une structure clé impliquée dans le traitement des émotions est l'**amygdale**. Il s'agit d'une région cérébrale profonde qui se trouve dans le lobe temporal médial, devant l'hippocampe. Son nom dérive du mot grec signifiant « amande », en référence à sa forme allongée.

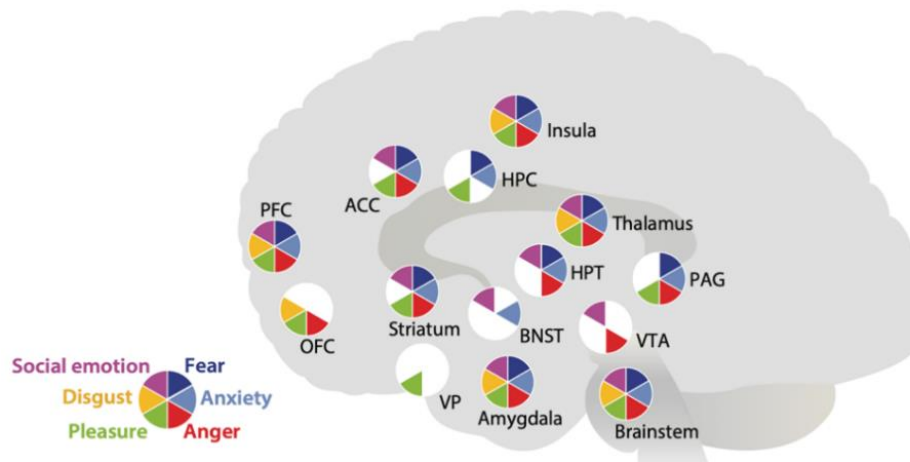
Cette région a traditionnellement été impliquée dans le traitement de la peur, comme suggéré par les études sur des patients avec des lésions bilatérales de l'amygdale (Adolphs et al., 1994; Feinstein et al., 2011). Déjà en 1994, LeDoux avait postulé deux circuits de la peur : un circuit « court », dans lequel un stimulus visuel est traité par le thalamus et atteint directement l'amygdale, permettant une réponse rapide ; et un circuit « long », qui du thalamus va au cortex préfrontal afin de contrôler l'action de l'amygdale et la réponse de peur (LeDoux, 1994) (voir la Figure 5). L'exemple classique pour illustrer la fonction de ces deux voies est l'anecdote du serpent : une personne qui se promène dans une forêt peut avoir une réponse immédiate de peur à la vue d'une forme allongée qui rappelle un serpent, et peu de temps après, une fois que l'information visuelle est traitée par le cortex, se rendre compte qu'il s'agit juste d'une branche d'arbre et par conséquent réguler sa réaction de peur, ce qui serait médié respectivement par le circuit court et le circuit long (LeDoux, 1997).



**Figure 5**

*Circuit cérébral de la peur, tirée de LeDoux, 1997. Ce schéma représente un circuit court, dans lequel les inputs sensoriels sont directement transmis au noyau latéral de l'amygdale, qui les relaie ensuite aux autres noyaux pour une réaction rapide, et un circuit long, où les informations passent par le cortex cérébral, permettant une régulation de la réponse de l'amygdale. Enfin, un troisième circuit, reliant l'hippocampe à l'amygdale, permet d'intégrer les souvenirs, modifiant ainsi la réponse émotionnelle en fonction de l'expérience passée.*

Nous savons aujourd'hui que l'amygdale n'est pas exclusivement liée à l'émotion de la peur, mais elle intervient également dans le traitement d'autres émotions telles que la colère ou la joie (Kirby & Robinson, 2017; Sergerie et al., 2008). En effet, sur le plan cérébral, concernant la relation structure - fonction nous pouvons parler de **pluripotentialité**, dans le sens où les régions cérébrales sont impliquées dans une multitude de fonctions, plutôt que d'avoir une correspondance spécifique et exclusive pour chaque émotion (Celeghein et al., 2017). Ainsi, les circuits neuronaux des différentes émotions se chevauchent en grande partie, même si des émotions différentes peuvent avoir des circuits mécanistiques différents (Malezieux et al., 2023, voir la Figure 6).

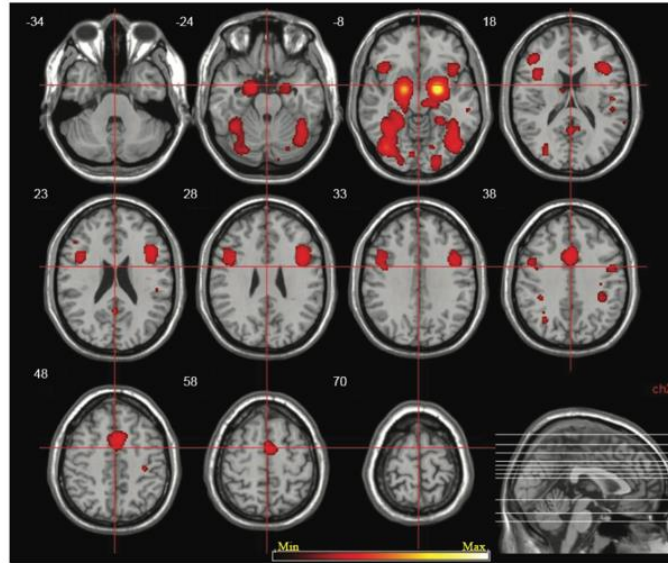


**Figure 6**

*Régions cérébrales associées au traitement des émotions, tirée de Malezieux et al., 2023. Ces régions sont fortement interconnectées et forment des réseaux fonctionnels essentiels à l'émergence et au traitement des émotions. Abréviations : ACC, cortex cingulaire antérieur ; BNST, noyau de la strie terminale ; HPC, hippocampe ; HPT, hypothalamus ; PFC, cortex préfrontal ; OFC, cortex orbitofrontal ; PAG, substance grise périaqueducule ; VP, pallidum ventral ; VTA, aire tegmentale ventrale.*

Dans une méta-analyse rassemblant les études en imagerie par résonance magnétique fonctionnelle (IRMf) qui ont comparé le traitement des visages (émotionnels et neutres) par rapport à une croix de fixation il a été montré une activation accrue dans plusieurs **régions visuelles** (gyrus fusiforme, gyrus occipital inférieur et moyen, gyrus lingual), des régions **limbiques** (amygdale et gyrus parahippocampique, cortex cingulaire postérieur), des régions **temporo-pariétales** (lobule pariétal, gyrus temporal moyen, insula), des régions **préfrontales** (gyrus frontal médian), des régions **sous-corticales** (putamen) et du **cervelet** (Fusar-Poli et al., 2009, voir la Figure 7).





**Figure 7**

*Circuits neurofonctionnels impliqués dans le traitement des visages émotionnels et neutres, tirée de Fusar-Poli et al., 2009. L'échelle de couleurs illustre les régions cérébrales présentant une activation significative lors d'une méta-analyse comparant des visages émotionnels et neutres à une croix de fixation.*

Historiquement, Bleuler et Kraepelin ont décrit les déficits émotionnels comme étant centraux dans la schizophrénie (Bleuler, 1911; Kraepelin, 1919). Cependant, la classification traditionnelle des symptômes en trois catégories (positifs, négatifs, désorganisation) ne prend pas en compte ces déficits de manière adéquate. Cela s'explique au moins en partie par la diversité des composantes émotionnelles affectées, telles que la perception, l'expression, l'expérience et la régulation des émotions. En effet, les patients atteints de schizophrénie présentent un profil singulier avec une perception émotionnelle altérée accompagnée d'une expression émotionnelle diminuée d'une part et une expérience émotionnelle renforcée d'autre part (Fakra et al., 2008), ainsi que des mécanismes de régulation émotionnelle dysfonctionnels (Ludwig et al., 2019).

En ce qui concerne l'expression émotionnelle, plusieurs travaux observent que les patients atteints de schizophrénie montrent un **émoussement affectif**, caractérisé par moins d'expressions faciales positives ou négatives en réponse à des stimuli émotionnels (Kring &

Moran, 2008). Cependant, les études d'expression spontanée montrent que leurs muscles faciaux réagissent de manière cohérente à la valence des stimuli (Kring & Elis, 2013).

Bien que les personnes vivant avec une schizophrénie expriment moins d'émotions, il a été constaté que leur expérience émotionnelle n'est pas réduite. Plusieurs études de laboratoire ont montré que les personnes atteintes de schizophrénie avaient bien une capacité d'expérimenter des émotions similaires à celle des sujets contrôles (Cohen & Minor, 2010). De plus, une méta-analyse sur des mesures écologiques observe même que les personnes vivant avec une schizophrénie rapportent **plus d'émotions négatives et moins d'émotions positives** dans leur vie de tous les jours (Cho et al., 2017).

La régulation émotionnelle a également montré être déficitaire dans la schizophrénie, et les patients atteints de schizophrénie semblent utiliser des **stratégies de régulation émotionnelle considérées comme moins adéquates**, tel que la rumination, l'auto-accusation et la distraction, alors qu'ils s'appuient moins sur la réévaluation cognitive (Ludwig et al., 2019).

Enfin, la perception émotionnelle est la composante du traitement émotionnel la plus étudiée. De nombreuses études ont montré que les personnes atteintes de schizophrénie présentent des déficits dans la perception émotionnelle. Ces déficits ont été le plus souvent étudiés dans le cadre de la **cognition sociale**, qui se réfère de façon plus générale aux opérations mentales qui sous-tendent les interactions sociales, y compris la perception, l'interprétation et la génération de réponses aux intentions, dispositions et comportements d'autrui (Green & Horan, 2010). L'une des principales composantes de la cognition sociale sont les moyens par lesquels nous déchiffrons une émotion sur le visage d'une autre personne, c'est-à-dire la **reconnaissance des émotions faciales**. La perception faciale, qui est définie comme tout traitement visuel de haut niveau des visages, implique à la fois un traitement perceptif - consistant à identifier la configuration géométrique des traits du visage pour discriminer différents stimuli en fonction de leur apparence- ainsi que la reconnaissance de la signification émotionnelle (Fusar-Poli et al., 2009).

Plusieurs méta-analyses ont montré que les patients atteints de schizophrénie présentent un déficit allant de modéré à sévère dans la reconnaissance d'émotions faciales (Chan et al., 2010; Kohler et al., 2010). Il a été suggéré que les patients auraient davantage de difficultés

dans l'identification d'expressions faciales d'émotions négatives, telles que la peur et la colère, même si certains résultats inconsistants existent dans la littérature (Gao et al., 2021).

Les déficits dans la reconnaissance des émotions faciales semblent être particulièrement associés aux symptômes négatifs de la schizophrénie (Ventura et al., 2013). En effet, ils ont montré être corrélés avec toutes les cinq catégories de symptômes négatifs (Andrzejewska et al., 2017) : l'anhédonie (la réduction de la capacité à ressentir du plaisir), l'avolition (la réduction des activités dirigées vers un but), le retrait social (la réduction des relations sociales), l'émoussement affectif (la réduction d'expressions faciales, vocales et corporelles des émotions), et l'alogie (la réduction et la pauvreté du discours) (Kirkpatrick et al., 2006).

Ces difficultés émotionnelles ont des répercussions significatives sur le **fonctionnement quotidien** des personnes atteintes de schizophrénie. Par exemple, une étude longitudinale a révélé une relation causale entre les performances des patients dans la perception émotionnelle et leur capacité à réussir dans le milieu du travail ainsi qu'à vivre de manière autonome (Kee et al., 2003). Ces déficits ne se limitent pas seulement à une réduction des capacités émotionnelles, mais impactent également le fonctionnement global des patients. Une méta-analyse a ainsi mis en évidence une corrélation positive entre la capacité à identifier les émotions et le pronostic fonctionnel des personnes atteintes de schizophrénie, en particulier dans les domaines nécessitant des compétences sociales (Irani et al., 2012).

Ce lien entre altérations émotionnelles et fonctionnement quotidien prend une importance particulière lorsqu'on considère la **valeur prédictive** de ces déficits pour le pronostic des patients. En effet, les capacités de reconnaissance émotionnelle se sont révélées être parmi les prédicteurs principaux des symptômes des maladies psychiatriques (Santamaría-García et al., 2020) et ils apparaissent comme des marqueurs ayant une valeur pronostique forte en ce qui concerne la réussite professionnelle, la capacité à vivre de manière indépendante et le fonctionnement social (Horan et al., 2012). De façon plus large, il a été proposé que les perturbations de la cognition sociale pourraient expliquer les difficultés à établir et à maintenir des relations interpersonnelles, entraînant ainsi des conflits interpersonnels et/ou un retrait social (Green & Horan, 2010).

Enfin, il est intéressant de noter que même si l'utilisation d'antipsychotiques, en particulier atypiques, pourrait jouer un rôle dans l'amélioration des performances des patients aux tâches de traitement des émotions faciales, la taille de l'effet rapportée est très faible et sa pertinence clinique a été questionnée, suggérant que ces déficits sont en large partie **indépendants des effets des médicaments** (Gabay et al., 2015). De plus, ces difficultés dans l'identification des émotions faciales apparaissent déjà aux stades précoces de la maladie, par exemple chez des personnes vivant un premier épisode psychotique (Barkl et al., 2014), ce qui souligne la **stabilité** de ce déficit même avant l'apparition de la forme chronique de la maladie.

Non seulement ces déficits sont retrouvés aux premiers stades de la maladie, mais les **apparentés sains de premier degré** des patients vivant avec une schizophrénie semblent également présenter des déficits dans la reconnaissance d'émotions faciales (Lavoie et al., 2013; Martin et al., 2020). En particulier, une méta-analyse de Martin et collaborateurs (2020) incluant 23 études a montré que les déficits seraient spécifiques aux émotions négatives, alors que selon cette méta-analyse il n'y aurait pas des preuves de déficits dans la reconnaissance des visages exprimant des émotions positives ou des visages neutres.

Ainsi, les déficits de reconnaissance émotionnelle observés chez les apparentés sains de patients atteints de schizophrénie, qui demeurent stables tout au long de la maladie et présentent des effets en partie distincts de ceux des médicaments, apparaissent comme un candidat prometteur pour être considérés comme un **endophénotype** de la schizophrénie.

## Le concept d'endophénotype

Selon le *Biomarkers Definitions Working Group* (2001), les biomarqueurs, ou marqueurs biologiques, font référence à des caractéristiques objectives et mesurables qui peuvent être utilisées comme un indicateur des processus biologiques normaux, des processus pathogéniques ou des réponses pharmacologiques à une intervention thérapeutique. Ces dernières années, un intérêt accru s'est porté vers un type spécifique de biomarqueur, connu sous le nom d'**endophénotype** ou de phénotype intermédiaire. Ce terme a été initialement emprunté au domaine de la biologie évolutionniste chez les insectes (John & Lewis, 1966) et introduit dans le champ de la psychiatrie par Gottesman et Shields (1972). Toutefois, ce n'est qu'au début des années 2000 que ce concept a été revisité et a commencé à avoir un impact significatif (Gottesman & Gould, 2003). La spécificité et l'intérêt d'étudier les endophénotypes résident dans le fait qu'il s'agit de composantes mesurables situées entre les symptômes observables de la maladie (le phénotype) et le fond génétique moléculaire sous-jacent (le génotype).

En particulier, selon Gottesman et Gould (2003), pour qu'un biomarqueur puisse être considéré comme un endophénotype, 5 critères principaux doivent être présents :

1. Un endophénotype est associé avec la maladie (il est plus fréquent chez les patients que chez les sujets contrôles) ;
2. Un endophénotype est héréditaire ;
3. Un endophénotype est état-indépendant, c'est-à-dire qu'il est stable tout au long de la vie d'un individu et se manifeste que la maladie soit présente ou non ;
4. Au sein des familles, l'endophénotype et la maladie co-ségrégent ;
5. L'endophénotype trouvé chez les membres de la famille affectés se retrouve chez les membres de la famille non affectés à un taux plus élevé que dans la population générale. Les apparentés montrent donc des valeurs de l'endophénotype intermédiaires entre leurs proches vivant avec une schizophrénie et des sujets contrôles.

La présence d'un sixième critère, concernant la spécificité de l'endophénotype pour la maladie d'intérêt (Gottesman & Shields, 1972), est plus controversée et dans les dernières années il a

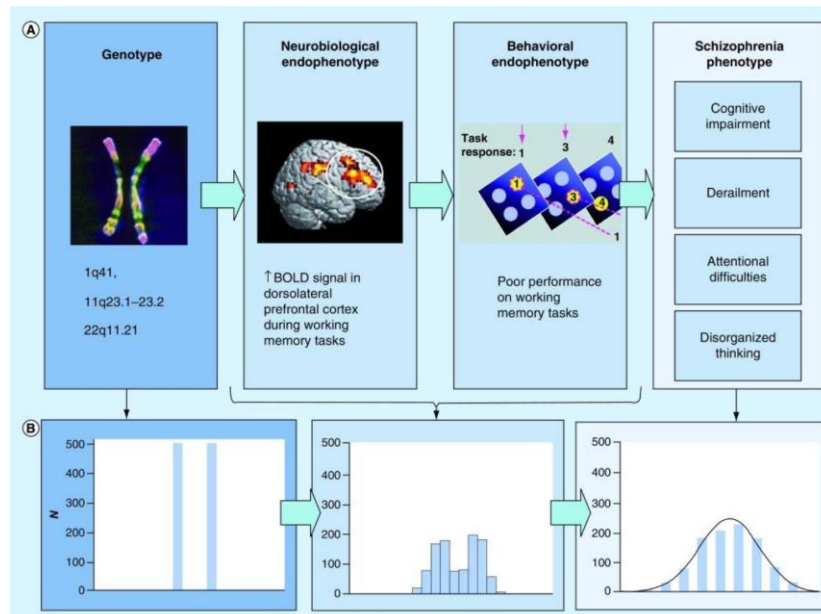
été suggéré que ce critère pourrait être écarté au vu du caractère souvent transdiagnostique des maladies psychiatriques (Beauchaine & Constantino, 2017). Dans ce contexte, la non-spécificité d'un endophénotype pourrait être vue comme une opportunité pour mettre en lumière des mécanismes psychopathologiques communs à plusieurs pathologies.

Par la suite, d'autres auteurs ont suggéré des critères supplémentaires pour définir des endophénotypes, tel qu'un lien avec une cause plutôt qu'avec une conséquence de la maladie, soulignant l'importance que le marqueur soit impliqué dans la pathogénie de la maladie (Bearden & Freimer, 2006).

La véritable force de cette approche basée sur la recherche d'endophénotypes repose sur l'idée que les gènes associés à des substrats neuronaux connus et en lien avec des déficits fonctionnels devraient être **plus facilement liés aux mécanismes biologiques** sous-jacents que les gènes associés à un phénotype clinique, plus complexe et flou (Swerdlow et al., 2015). Cela est particulièrement intéressant dans le cadre de la schizophrénie, où les résultats des efforts communs à grande échelle ont souligné la complexité des mécanismes impliqués et le caractère fortement polygénique de la maladie (Sullivan et al., 2024), ainsi que sa large hétérogénéité. Bien que plusieurs variations génétiques aient été associées à la maladie jusqu'à ce jour, il reste difficile d'établir des liens **causaux**, ainsi que de traduire ces connaissances dans une application clinique. Ainsi, certains soulignent que l'approche « *data-driven* » des GWAS présente à la fois des avantages et des défis. Bien que cette approche offre une précision rigoureuse dans l'identification des variations génétiques communes, elle peut également masquer une grande incertitude, notamment en ignorant les connaissances neurobiologiques préexistantes (Braff, 2015). Dans ce contexte, l'étude des endophénotypes peut nous aider à élucider les voies étiologiques qui sous-tendent l'apparition de la schizophrénie.

De plus, les endophénotypes reflètent des traits qui se distribuent de manière continue dans la population générale. Ainsi, en utilisant les endophénotypes pour mesurer la prédisposition sous-jacente à la maladie comme un **trait quantitatif et continu**, il y a un gain de puissance statistique, puisque plutôt que de simplement dire qu'une personne a ou n'a pas la maladie, on peut mesurer des aspects spécifiques du fonctionnement cognitif ou du cerveau qui sont liés au risque de développer la maladie. Cette mesure plus fine permet de capter davantage

de nuances et de variations dans la population (Greenwood et al., 2019). Voir la Figure 8 pour un résumé graphique du concept d'endophénotype.



**Figure 8**

*Représentation de la chaîne qui du génotype amène au phénotype, tirée de Beauchaine et Constantino, 2017. Les endophénotypes (neurobiologiques et comportementales) se trouvent au milieu de cette chaîne (A.). Ils montrent une meilleure précision de mesure facilitant l'identification des génotypes (B.).*

Les endophénotypes sont considérés comme des mesures clés dans le cadre de la nouvelle approche de recherche sur les maladies mentales de l'RDoC, car ils offrent des cibles intermédiaires pour mieux comprendre les troubles mentaux. En effet, ces endophénotypes, qui sont des caractéristiques biologiques ou psychologiques mesurables, sont plus proches des bases génétiques que les catégories diagnostiques traditionnelles (Braff, 2015). En outre, les endophénotypes pourraient permettre de créer des sous-groupes plus simples et homogènes, aidant ainsi à surmonter les limites liées à l'hétérogénéité des troubles mentaux (Braff, 2015).

Plusieurs endophénotypes neurocognitifs de la schizophrénie ont déjà été proposés, notamment par le *Consortium on the Genetics of Schizophrenia*, une collaboration multisite sponsorisée par le NIMH qui a été mise en place avec l'objectif de valider des endophénotypes dans la schizophrénie (Gur et al., 2007). Ce consortium a sélectionné 12 potentiels endophénotypes neurocognitifs et neurophysiologiques avec une sélection a priori basée sur la littérature, en prenant en compte les critères suivants : associé à la maladie, état-indépendant, avec une stabilité test-retest, avec une fiabilité inter-sites adéquate, et avec des preuves que les effets observés ne sont pas liés au traitement (Gur et al., 2007). Parmi les endophénotypes considérés comme les plus robustes, on retrouve l'attention (comme l'attention soutenue mesurée par le *Continuous Performance Task* -demandant aux participants de répondre à des stimuli cibles spécifiques tout en ignorant les distractions), la mémoire verbale (mesuré par le *California Verbal Learning Test* -demandant aux participants de mémoriser et de rappeler une liste de mots sur plusieurs essais) et la mémoire de travail (mesuré par le *Letter-Number span test* -où le participant doit organiser une série de lettres et de chiffres en les classant dans l'ordre numérique puis alphabétique) (Gur et al., 2007). De plus, dans ces travaux préliminaires sur les endophénotypes dans la schizophrénie, l'importance d'étudier le traitement émotionnel, et en particulier la **reconnaissance d'émotions faciales**, comme candidat potentiel de la schizophrénie a été mise en avant (Gur et al., 2007). Ces travaux préliminaires se sont basés sur le *Penn Emotion Recognition Test-40* (Kohler et al., 2003), faisant partie de la *Penn Computerized Neurocognitive Battery*. Dans cette tâche, le participant voit des visages émotionnels et neutres et doit évaluer la valence émotionnelle de chaque expression.

Plusieurs endophénotypes peuvent exister, et la validation de différents types doit être considérée comme un atout, permettant de les combiner pour mieux caractériser la maladie et, éventuellement, distinguer différents sous-types de patients ayant des mécanismes neurobiologiques distincts.

Selon certains auteurs, les endophénotypes issus de la neuroimagerie sont à privilégier puisqu'ils sont reproductibles, fournissent des données quantitatives et sont souvent bien plus sensibles que les observations comportementales aux changements subtils (Hariri & Weinberger, 2003). De plus, les déficits comportementaux peuvent varier au cours de la



maladie, alors que les dysfonctionnements cérébraux sont supposés être plus stables (Gur et al., 2007). Passer des critères diagnostiques à une compréhension des circuits cérébraux pourrait ouvrir la voie au développement de thérapies ciblées pour traiter des vulnérabilités neurobiologiques spécifiques, ce qui serait particulièrement pertinent pour les patients résistants aux traitements (Donati et al., 2020).

Comme le montrent les études du *Consortium on the Genetics of Schizophrenia*, les recherches sur **les apparentés de premier degré** des patients, qui, au contraire de leurs frères ou sœurs malades, ne présentent pas de diagnostic, permettent de mettre en lumière des endophénotypes. En effet, les apparentés de premier degré partagent une partie de la vulnérabilité génétique avec leurs frères ou sœurs atteints de schizophrénie (puisqu'ils partagent environ 50 % de leurs gènes), mais n'ont pourtant pas développé la maladie. Cela permet d'étudier le risque de schizophrénie sans l'influence de facteurs confondants tels que le traitement médicamenteux et les séquelles de la chronicité de la maladie.

Le taux de transition vers la schizophrénie pour les apparentés de premier degré a été estimé à 13 % après un an (Hormozpour et al., 2016), ce qui implique qu'une proportion significative d'entre eux ne développera pas la maladie. Plusieurs facteurs pourraient expliquer cela, et il est parfois difficile de les distinguer. Par exemple, ces individus pourraient présenter des facteurs de risque génétiques et non génétiques, mais à des niveaux insuffisants pour déclencher la schizophrénie. Il est également possible que ces facteurs de risque génétiques interagissent avec des facteurs protecteurs génétiques ou des influences environnementales (Braff, 2015).

## OBJECTIF DE LA THESE

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Comme nous l'avons vu, la schizophrénie est une maladie psychiatrique complexe qui représente un lourd fardeau tant au niveau individuel que sociétal. Bien que notre compréhension des causes de la maladie soit encore limitée, il est établi que des facteurs génétiques interagissent avec des facteurs environnementaux pour déterminer une vulnérabilité à la schizophrénie. Cependant, cette pathologie est caractérisée par une complexité polygénique, rendant difficile l'établissement de relations directes entre les gènes et la maladie. Une approche émergente, proposée pour surmonter en partie ces difficultés, consiste à étudier les endophénotypes. Ces caractéristiques mesurables, situées entre les gènes et le comportement, se manifestent également, bien que de manière atténuée, chez les apparentés sains des patients, qui partagent environ 50 % de la prédisposition génétique à la maladie. Dans le cadre des maladies psychiatriques, les endophénotypes les plus solides se trouvent au niveau du fonctionnement cérébral. En effet, étant donné que les gènes sont impliqués dans le développement du cerveau, les variations génétiques peuvent influencer différemment le développement et le fonctionnement des systèmes neuronaux, ce qui peut entraîner des réponses comportementales variables.

Parmi les potentiels candidats comme endophénotypes de la schizophrénie, la perception émotionnelle émerge comme particulièrement pertinente, bien qu'elle ait été moins explorée. En effet, des déficits dans la reconnaissance émotionnelle ont été observés chez les apparentés sains de patients atteints de schizophrénie, avec des tailles d'effet moindres par rapport à celles observées chez les patients eux-mêmes. De plus, ces déficits semblent fortement corrélés avec le pronostic fonctionnel des patients, suggérant une influence causale potentielle dans le déclenchement de la maladie. Ainsi, l'objectif de cette thèse est d'étudier les corrélats cérébraux de la perception émotionnelle en tant que potentiel endophénotype de la schizophrénie.

Dans le **Chapitre I**, nous avons fait, à travers une approche méta-analytique, une synthèse des connaissances actuelles sur le rôle potentiel des activations cérébrales en réponse aux stimuli émotionnels en tant qu'endophénotype de la schizophrénie. Nous avons rassemblé toutes les études ayant utilisé des tâches émotionnelles en IRMf chez des individus à risque de

développer la schizophrénie, incluant des apparentés, des individus à haut risque clinique et des individus avec des traits schizotypiques élevés. Nous avons examiné les activations cérébrales en réponse aux stimuli négatifs par rapport aux stimuli neutres, qui sont le plus souvent utilisés dans la littérature, ainsi qu'à une condition contrôle (c'est-à-dire une tâche de référence). En adoptant une double approche, fréquentiste et bayésienne, nous avons démontré qu'il existe des preuves solides en faveur de **l'absence de différences dans l'activation cérébrale** en réponse aux stimuli négatifs chez ces individus à risque, notamment dans les régions limbiques telles que l'amygdale. Nous avons souligné l'importance d'examiner la **connectivité cérébrale** pour mieux comprendre les relations complexes entre les régions impliquées dans le traitement émotionnel.

Dans le **Chapitre II**, nous nous sommes interrogés sur la pertinence des stimuli neutres, classiquement utilisés comme comparateurs des stimuli émotionnels dans les études en IRMf. Nous avons mené une méta-analyse des études investiguant l'activation cérébrale en réponse à des visages neutres par rapport à une condition contrôle ou à une croix de fixation chez des apparentés de premier degré de patients atteints de schizophrénie. Nos résultats ont mis en lumière une hypoactivation des régions limbiques chez ces individus à risque génétique, comparativement aux sujets contrôles. Nous avons proposé que, dans le contexte des hyperactivations aux stimuli neutres observées chez les patients atteints de schizophrénie, cette hypoactivation pourrait représenter un **facteur protecteur**. Nous avons suggéré que les futures études en IRMf portent une **attention particulière à l'utilisation des stimuli neutres** lorsqu'elles explorent la composante émotionnelle.

Dans le **Chapitre III**, nous avons évalué la validité des corrélats cérébraux du traitement émotionnel en tant qu'endophénotype de la schizophrénie à l'aide d'une étude en IRMf chez des patients atteints de schizophrénie, leurs frères et sœurs, ainsi que des sujets contrôles. Nous avons utilisé une tâche de reconnaissance émotionnelle plus écologique que celles couramment décrites dans la littérature, en manipulant des visages exprimant des émotions associées à des scènes d'arrière-plan, également émotionnels. En utilisant une double approche fréquentiste et bayésienne, nos résultats ont mis en évidence l'absence de différences significatives entre les patients atteints de schizophrénie et leurs apparentés par rapport aux sujets contrôles dans la majorité des régions cérébrales, y compris dans des

structures limbiques telles que l'amygdale. Cependant, nous avons identifié chez les apparentés une hypoactivation du cortex somatosensoriel, s'étendant au gyrus temporal supérieur, avec une activation réduite également observée chez les patients atteints de schizophrénie, comme montré par les statistiques bayésiennes. Enfin, nous avons montré une connectivité fonctionnelle anormalement élevée chez les apparentés entre l'amygdale droite et le cuneus droit lors de la perception de visages exprimant des émotions négatives, par rapport aux patients et aux sujets contrôles. Nous avons discuté de l'interprétation de ces résultats en relation avec leur pertinence en tant qu'**endophénotype** de la schizophrénie, ainsi qu'en considérant les **éventuels facteurs de protection et mécanismes compensatoires** qui pourraient être à l'œuvre chez les apparentés des patients.

Dans le **Chapitre IV**, nous nous sommes intéressés à la composante génétique des endophénotypes. En effet, certaines variations génétiques, notamment celles impliquées dans les processus neurodéveloppementaux et immunitaires, pourraient influencer les endophénotypes, tels que la perception émotionnelle. Nous avons exploré le rôle crucial de la microglie, un type de cellule gliale participant à l'immunité cérébrale, à l'élagage synaptique et potentiellement à la régulation des émotions, en tant qu'élément central dans la physiopathologie de la schizophrénie. Nous avons montré comment les **altérations microgliales, tant au niveau cérébral que périphérique**, pourraient refléter des mécanismes dysfonctionnels dans la schizophrénie, contribuant ainsi à une meilleure compréhension des processus biologiques sous-jacents à cette maladie.

Enfin, dans les **perspectives futures**, nous avons suggéré de **nouvelles pistes pour la recherche d'endophénotypes** dans la schizophrénie, articulées autour de trois axes : explorer des facettes plus complexes du traitement émotionnel, adopter un modèle multidimensionnel capable de relier la composante génétique aux dysfonctionnements cérébraux, et favoriser une approche plus transdiagnostique, tenant compte de l'importante hétérogénéité de la maladie. Face à un diagnostic souvent tardif et sans rémission, cette recherche contribuera à une meilleure compréhension des mécanismes sous-jacents, avec l'espoir de valider des endophénotypes qui pourraient un jour être appliqués en clinique. Cela permettrait un dépistage plus précoce, ouvrant la voie à la mise en place de stratégies d'intervention adaptées et au développement d'approches thérapeutiques plus ciblées.

## CHAPITRE I - Peut-on considérer l'activation cérébrale en réponse à des stimuli émotionnels comme un endophénotype de la schizophrénie ?

### [Article #1]

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Un nombre considérable d'études en IRMf s'est intéressé aux corrélats cérébraux du traitement émotionnel dans la schizophrénie, et plusieurs méta-analyses ont été publiées afin de résumer les résultats, souvent hétérogènes, des études individuelles. La majorité de ces méta-analyses rapportent une **réduction de l'activation cérébrale** dans l'amygdale bilatérale (Anticevic et al., 2012; Delvecchio et al., 2013; Dong et al., 2018; Jáni & Kašpárek, 2018; Li et al., 2010; Taylor et al., 2012). D'autres régions qui ont souvent été rapportées sont le gyrus parahippocampal (Delvecchio et al., 2013; Dong et al., 2018; Li et al., 2010), et le gyrus fusiforme (Delvecchio et al., 2013; Dong et al., 2018; Li et al., 2010; Taylor et al., 2012). Toutefois, les résultats varient entre ces méta-analyses et, par exemple, si certaines études rapportent une réduction de l'activation du cortex cingulaire antérieur (Delvecchio et al., 2013; Jáni & Kašpárek, 2018; Taylor et al., 2012), d'autres observent une activation augmentée (Dong et al., 2018). Cela est vraisemblablement dû en grande partie à une hétérogénéité méthodologique entre ces méta-analyses, concernant essentiellement les tâches, les stimuli et les contrastes d'IRMf utilisés.

À ce jour, il existe beaucoup moins d'études en neuroimagerie portant sur les corrélats cérébraux du traitement émotionnel chez les individus à risque, et les résultats sont moins cohérents que chez les patients vivant avec une schizophrénie. Par conséquent, nous avons conduit une **étude méta-analytique** afin de rassembler nos connaissances actuelles et de clarifier si les individus à risque présentent une **activité cérébrale** différente en réponse **aux stimuli émotionnels** par rapport aux sujets contrôles ([Article #1](#), Fiorito et al., *Biol Psychiatry*, 2022). Nous nous sommes intéressés à trois populations considérées comme ayant un risque accru de développer une schizophrénie : les apparentés de premier degré des patients vivant avec une schizophrénie, les individus à haut risque clinique, ainsi que les individus avec des traits de schizotypie élevés.

Nous avons employé des techniques de pointe, en utilisant les cartes statistiques non seuillées du cerveau entier, plutôt que de simples coordonnées. Les résultats des analyses fréquentistes

sur l'ensemble du cerveau, obtenus en implémentant un modèle à effets aléatoires dans le logiciel Seed-based d Mapping, ont été complétés par des analyses bayésiennes. Cette dernière analyse a permis de quantifier les preuves en faveur de l'hypothèse nulle (absence de différence entre les groupes) ainsi que de l'hypothèse alternative (existence d'une différence entre les groupes). Pour les deux cadres statistiques, nous avons d'abord examiné séparément les réponses cérébrales aux stimuli émotionnels chez les personnes à risque et les sujets contrôles (analyse intra-groupe), puis chez les personnes à risque versus les sujets contrôles (analyse inter-groupe). Enfin, à la lumière des résultats précédents chez les patients, l'activité de l'amygdale a été scrutée à l'aide d'analyses par régions d'intérêt.

Dix-sept études ont été incluses, portant sur un total de **677 individus à risque et 807 sujets contrôles**. La méta-analyse fréquentiste intra-groupe a montré une activation dans les régions cérébrales attendues, incluant l'amygdale, le thalamus et le gyrus frontal inférieur, avec un pattern remarquablement similaire pour les individus à risque et les sujets contrôles. La méta-analyse bayésienne intra-groupe a largement reproduit les résultats des analyses fréquentistes. La méta-analyse fréquentiste inter-groupe n'a révélé aucune différence significative entre les individus à risque et les sujets contrôles. La méta-analyse bayésienne inter-groupe a fourni des preuves solides soutenant l'**absence de différence entre les groupes dans l'ensemble du cerveau**, avec seulement deux clusters de petite taille dans le gyrus frontal supérieur gauche et la matière blanche montrant une preuve modérée d'une augmentation de l'activité cérébrale chez les personnes à risque par rapport aux sujets contrôles. Les analyses bayésiennes dans l'amygdale ont confirmé l'absence de différence entre les groupes. Les résultats sont restés inchangés lorsqu'on a inclus séparément les différents groupes d'individus à risque (apparentés, individus à haut risque clinique ou individus avec des traits de schizotypie élevés), et les différents contrastes d'IRMf (stimuli négatifs versus stimuli neutres ou versus une condition contrôle/croix de fixation). Les analyses de sensibilité ont indiqué une faible hétérogénéité et aucune preuve de biais de publication.

Cette méta-analyse suggère qu'il n'y a pas de différences dans les réponses cérébrales aux stimuli émotionnels entre les individus à risque de schizophrénie et les sujets contrôles. Ainsi, ces résultats apportent des arguments contre la conceptualisation des réponses aux stimuli émotionnels comme un endophénotype de la schizophrénie. Cependant, étant donné que les

émotions sont traitées par un système de structures distribuées et interconnectées, de futures études pourraient bénéficier de l'exploration de la **connectivité cérébrale** des régions impliquées dans le traitement émotionnel chez les personnes à risque de schizophrénie.

#### Article #1

Are Brain Responses to Emotion a Reliable Endophenotype of Schizophrenia? An Image-Based Functional Magnetic Resonance Imaging Meta-analysis

Anna M. Fiorito, André Aleman, Giuseppe Blasi, Josiane Bourque, Hengyi Cao, Raymond C.K. Chan, Asadur Chowdury, Patricia Conrod, Vaibhav A. Diwadkar, Vina M. Goghari, Salvador Guinjoan, Raquel E. Gur, Ruben C. Gur, Jun Soo Kwon, Johannes Lieslehto, Paulina B. Lukow, Andreas Meyer-Lindenberg, Gemma Modinos, Tiziana Quarto, Michael J. Spilka, Venkataram Shivakumar, Ganesan Venkatasubramanian, Mirta Villarreal, Yi Wang, Daniel H. Wolf, Je-Yeon Yun, Eric Fakra\*, Guillaume Sescousse\*.

*Biological Psychiatry*, 93, 167–177 (2022). <https://doi.org/10.1016/j.biopsych.2022.06.013>

Preprint available on MedRxiv

(<https://www.medrxiv.org/content/10.1101/2022.05.31.22275506v1>)

# Résumé graphique Article #1 - présenté au congrès de l'OHBM, Glasgow (Ecosse), Juin 2022



## EMOTIONAL BRAIN RESPONSES: AN ENDOPHENOTYPE OF SCHIZOPHRENIA?

### An image-based fMRI meta-analysis

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### BACKGROUND



Behaviour:

- Patients with **schizophrenia** show impairments in **emotion perception**
- Abnormal emotion perception is also observed in people at **risk of schizophrenia**

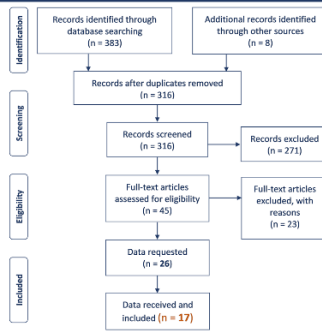


Cerebral correlates:

- Cortico-limbic system is impaired in patients with schizophrenia (**decreased amygdala activation**)
- Is brain activation during emotion perception an **endophenotype** of schizophrenia?

### METHODS

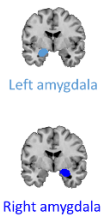
- **Image-based meta-analysis** with unthresholded T-maps as input
- Pubmed, Web of Science
- **Emotional vs non emotional contrast**
- **805 healthy controls, 677 people at risk**
- **Subgroup analyses:**
  - 1- type of risk (familial risk, clinical high risk or psychometric risk)
  - 2- type of task (implicit or explicit)
  - 3- type of contrast (emotion vs neutral stimuli or control condition/implicit baseline)



#### Whole-brain analyses

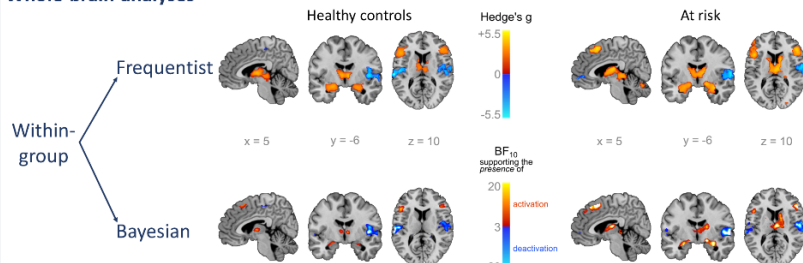
- Within-group:
  - Frequentist (SDM-PSI)
  - Bayesian (BayesFactorfMRI)
- Between-group:
  - Frequentist (SDM-PSI)
  - Bayesian (BayesFactorfMRI)

#### ROI analyses



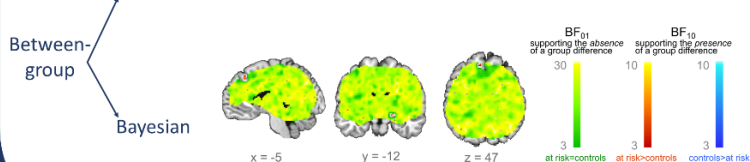
### RESULTS

#### Whole-brain analyses



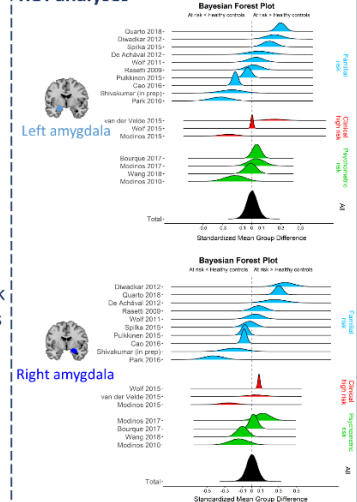
- **Similar pattern of brain activation** in healthy controls and people at risk
- **Bayesian analyses** largely reproduce the pattern of **frequentist analyses**

Between-group: Frequentist  $\emptyset$  No significant results (also for subgroup analyses)



- Bayesian analyses provide evidence in favour of the **absence of brain activation differences** between people at risk and healthy controls

#### ROI analyses



- Absence of group differences in the amygdala
- No apparent differences between type of risk subgroups

### CONCLUSIONS

- People at risk have **neurotypical brain responses** during emotion perception
- There is **no difference** in brain activation during emotion perception between people at risk and healthy controls
- Brain activation during emotion perception is **not an endophenotype** of schizophrenia



# Are Brain Responses to Emotion a Reliable Endophenotype of Schizophrenia? An Image-Based Functional Magnetic Resonance Imaging Meta-analysis

Anna M. Fiorito, André Aleman, Giuseppe Blasi, Josiane Bourque, Hengyi Cao, Raymond C.K. Chan, Asadur Chowdury, Patricia Conrod, Vaibhav A. Diwadkar, Vina M. Goghari, Salvador Guinjoan, Raquel E. Gur, Ruben C. Gur, Jun Soo Kwon, Johannes Lieslehto, Paulina B. Lukow, Andreas Meyer-Lindenberg, Gemma Modinos, Tiziana Quarto, Michael J. Spilka, Venkataram Shivakumar, Ganesan Venkatasubramanian, Mirta Villarreal, Yi Wang, Daniel H. Wolf, Je-Yeon Yun, Eric Fakra, and Guillaume Sescousse

## ABSTRACT

**BACKGROUND:** Impaired emotion processing constitutes a key dimension of schizophrenia and a possible endophenotype of this illness. Empirical studies consistently report poorer emotion recognition performance in patients with schizophrenia as well as in individuals at enhanced risk of schizophrenia. Functional magnetic resonance imaging studies also report consistent patterns of abnormal brain activation in response to emotional stimuli in patients, in particular, decreased amygdala activation. In contrast, brain-level abnormalities in at-risk individuals are more elusive. We address this gap using an image-based meta-analysis of the functional magnetic resonance imaging literature.

**METHODS:** Functional magnetic resonance imaging studies investigating brain responses to negative emotional stimuli and reporting a comparison between at-risk individuals and healthy control subjects were identified. Frequentist and Bayesian voxelwise meta-analyses were performed separately, by implementing a random-effect model with unthresholded group-level T-maps from individual studies as input.

**RESULTS:** In total, 17 studies with a cumulative total of 677 at-risk individuals and 805 healthy control subjects were included. Frequentist analyses did not reveal significant differences between at-risk individuals and healthy control subjects. Similar results were observed with Bayesian analyses, which provided strong evidence for the absence of meaningful brain activation differences across the entire brain. Region of interest analyses specifically focusing on the amygdala confirmed the lack of group differences in this region.

**CONCLUSIONS:** These results suggest that brain activation patterns in response to emotional stimuli are unlikely to constitute a reliable endophenotype of schizophrenia. We suggest that future studies instead focus on impaired functional connectivity as an alternative and promising endophenotype.

<https://doi.org/10.1016/j.biopsych.2022.06.013>

Schizophrenia is a chronic and profoundly disabling psychiatric disorder that has a significant effect on patients' well-being (1). A core feature of the disorder is impairment in emotion processing, in particular, poorer emotion recognition performance. Indeed, numerous studies show that patients with schizophrenia have deficits in emotion perception, particularly during facial emotion processing (2,3). Moreover, these deficits may play a key role in schizophrenia's etiopathogenesis (4). It has been proposed that vulnerability to schizophrenia itself could be linked to an overall tendency to experience more negative affect (5). Behavioral deficits have also been accompanied by functional brain abnormalities: several meta-analyses have described atypical blood oxygen level-dependent activation in patients with schizophrenia compared with healthy control subjects during emotion

perception (6–12). The most consistent finding is a hypo-activation of the amygdala during emotion processing (6–11).

Individuals at enhanced risk of schizophrenia (hereafter called "at risk" individuals) tend to show similar but more subtle behavioral deficits when processing emotions (13). Meta-analyses show moderate abnormalities in emotion recognition in healthy first-degree relatives (14,15) [who share part of the genetic vulnerability and therefore are considered at familial risk (16)] and individuals at clinical high risk (CHR) (17) [who are considered at risk based on clinical criteria (18)]. Evidence for these abnormalities is particularly notable for negative emotions (15). In a similar vein, individuals with high schizotypy traits based on self-report questionnaires [psychometric risk (19)] experience more difficulties in recognizing emotions than individuals with low schizotypy traits (20). Therefore, it has reasonably been proposed

that these deficits could represent a candidate endophenotype of schizophrenia (21), a measurable component along the pathway between the disease and the distal genotype, but less readily observed in at-risk individuals (22).

Neuroimaging measures are considered as particularly informative endophenotypes (23,24) because they may be more stable than behavioral performance, which varies considerably throughout the course of the illness (21). However, there is a relative paucity of results from neuroimaging studies investigating emotion processing in at-risk individuals, and observed differences in activation-based measures are inconsistent. Moreover, individual studies have been characterized by relatively modest sample sizes, hence providing limited statistical power (25). Several studies have relied on region of interest (ROI) approaches, thus failing to provide information on whole-brain differences in brain activation (26,27). Some studies have reported decreased activation in the amygdala (28–30), partially consistent with the literature on schizophrenia. However, there are several concurrent reports of hyperactivation of the amygdala (31,32) or of null results (33–35). Meta-analyses are ideally suited for disambiguating such confusion, and 2 of them have actually been performed in an attempt to quantify brain abnormalities during the processing of emotional stimuli in healthy first-degree relatives (36) and CHR individuals (37). While no significant differences were found in the latter group (37), widespread clusters of hyperactivation were found in healthy first-degree relatives (36). However, owing to the small number of included studies ( $n = 4$ ) (36,37), these meta-analyses had limited statistical power, motivating the need of a more powerful meta-analysis.

Indeed, this uncertainty clouds our ability to properly assess the value of activation-based differences during emotion processing as reliable endophenotypes in the schizophrenia diathesis (38). Accordingly, our main objective was to clarify whether at-risk individuals exhibit abnormal brain responses to negative emotional stimuli compared with healthy control subjects. To investigate this question, we performed an image-based meta-analysis, using functional neuroimaging data acquired across multiple studies. Whole-brain frequentist analyses, implemented using a random-effect model in the seed-based  $d$  mapping (SDM) software, and Bayesian analyses were performed. This latter approach allowed us to quantify evidence in favor of the null hypothesis (absence of a group difference) and the alternative hypothesis (existence of a group difference). In both statistical frameworks, we first examined brain responses to negative emotional stimuli versus nonemotional stimuli (i.e., neutral stimuli, control condition, or implicit baseline) separately in at-risk individuals (i.e., familial risk, CHR, psychometric risk) and healthy control subjects (within-group meta-analysis), and then in at-risk individuals versus healthy control subjects (between-group meta-analysis). Finally, in light of previous findings in patients, activation differences in the amygdala were specifically investigated via ROI analyses.

## METHODS AND MATERIALS

### Inclusion of Studies

The meta-analysis was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (39) (see Table S1 for the checklist).

The protocol for this meta-analysis was not preregistered. We performed a comprehensive literature search using PubMed and Web of Science. The search (which identified records published until April 15, 2020) used a combination of terms constructed according to 4 stems relating to 1) schizophrenia (schizophren\*, psychosis), 2) at-risk individuals (relatives, first-degree, siblings, twins, brothers, sisters, offspring, parents, high risk, ultrahigh risk, ultra-high risk, genetic risk, clinical risk, prodromal, ARMS, at-risk mental state), 3) neuroimaging (neuroimaging, functional magnetic resonance imaging, fMRI), and 4) emotions (emotion\*, affect, mood). Moreover, an inspection of the reference lists of included studies was performed to find articles that were not identified through the database search.

Inclusion criteria were the following: studies that 1) were written in English, 2) reported a comparison between at-risk individuals (i.e., familial risk, CHR, psychometric risk) and healthy control subjects, 3) used task-based functional magnetic resonance imaging (fMRI) with an emotion perception element, and 4) included negatively valenced emotional stimuli. We focused on negative stimuli because this class of stimuli is more heavily represented in emotional tasks and appears to induce stronger behavioral impairments in individuals at enhanced risk than positive stimuli (15).

The following exclusion criteria were applied: studies that 1) did not report an emotional versus nonemotional contrast and for which the authors could not provide the desired contrast when queried, 2) used a paradigm nonspecific to emotion processing (e.g., conditioning paradigm, theory of mind paradigm), 3) did not mainly use visual emotional stimuli of faces or scenes in their protocol, 4) primarily used positively valenced emotional stimuli, 5) did not use unique populations (i.e., used data from another included study), since inclusion of results that are not statistically independent can inflate type I error (40), 6) could not provide a whole-brain analysis, 7) could only provide a general  $F$  statistic instead of direct comparisons between groups, 8) were published conference papers, and 9) were systematic reviews or meta-analyses.

The literature search yielded a total of 308 unique articles (Figure S1). Initial screening based on title or abstract was performed (by AMF). After these exclusions, 45 full articles were independently screened (by AMF and GS) to be assessed for eligibility. Disagreements were resolved through discussion and mediation by a third author (EF). Our strict application of inclusion and exclusion criteria filtered the analysis to a total of 26 unique articles. The corresponding authors on these 26 articles were contacted to obtain unthresholded group-level  $T$ -maps, associated with within- and between-groups effects. Following this correspondence, we included data for 16 studies. Data from the remaining studies could not be included (31,41–49) either because corresponding authors were not responsive (after multiple reminders), the required data were lost and/or impossible to retrieve, or the data were found to be dubious (see Supplemental Methods for more details on study exclusion). Our correspondence also revealed the existence of a yet unpublished study meeting all inclusion criteria (unpublished data, V. Shivakumar, M.B.M.S., Ph.D., *et al.*<sup>1</sup>), bringing the number of included studies to a total of 17.

<sup>1</sup>The recruitment of participants for this unpublished study started in February 2012 and ended in June 2016.

Table 1. Included Studies

| Reference                               | Definition of At Risk   | Number of Participants |                 | Task Used                | Explicit/implicit Task | Type of Stimuli                                       | Contrast Included  |
|---|-------------------------|------------------------|-----------------|--------------------------|------------------------|---|--|
|   |                         | At Risk                | HC              |                          |                        |   |  |
| Bourque <i>et al.</i> , 2017 (76)       | Psychometric            | 27                     | 135             | Passive viewing          | Implicit               | Faces   | Angry stimuli > control condition                                |
| Cao <i>et al.</i> , 2016 (55)           | Familial (first-degree) | 58                     | 94              | Emotion matching         | Explicit               | Faces   | Negative stimuli > control condition                             |
| de Achával <i>et al.</i> , 2012 (77)    | Familial (siblings)     | 14                     | 14              | Gender recognition       | Implicit               | Faces   | Positive and negative stimuli > implicit baseline <sup>a,b</sup> |
| Diwadkar <i>et al.</i> , 2012 (26)      | Familial (offsprings)   | 17                     | 25 <sup>c</sup> | Emotion recognition      | Explicit               | Faces   | Negative stimuli > neutral stimuli <sup>a</sup>                  |
| Modinos <i>et al.</i> , 2010 (67)       | Psychometric            | 17                     | 17              | Emotion regulation       | Explicit               | IAPS (complex scenes of people)                       | Negative stimuli > neutral stimuli <sup>a</sup>                  |
| Modinos <i>et al.</i> , 2015 (29)       | CHR                     | 18                     | 20              | Emotional arousal rating | Explicit               | IAPS (complex scenes of people, animals, and objects) | Negative stimuli > neutral stimuli <sup>a</sup>                  |
| Modinos <i>et al.</i> , 2017 (35)       | Psychometric            | 21                     | 22              | Emotional arousal rating | Explicit               | IAPS (complex scenes of people, animals, and objects) | Negative stimuli > neutral stimuli <sup>a</sup>                  |
| Park <i>et al.</i> , 2016 (28)          | Familial (first-degree) | 20                     | 17              | Gender recognition       | Implicit               | Faces   | Fearful stimuli > implicit baseline                              |
| Pulkkinen <i>et al.</i> , 2015 (78)     | Familial (offsprings)   | 51                     | 52              | Passive viewing          | Implicit               | Faces   | Fearful stimuli > control condition                              |
| Quarto <i>et al.</i> , 2018 (74)        | Familial (siblings)     | 36                     | 56              | Gender recognition       | Implicit               | Faces   | Fearful stimuli > neutral stimuli <sup>a</sup>                   |
| Rasetti <i>et al.</i> , 2009 (79)       | Familial (siblings)     | 29                     | 20              | Emotion matching         | Explicit               | Faces   | Negative stimuli > control condition                             |
| Shivakumar <i>et al.</i> <sup>d</sup>   | Familial (first-degree) | 13                     | 15              | Emotion matching         | Explicit               | Faces   | Negative stimuli > control condition                             |
| Spilka <i>et al.</i> , 2015 (33)        | Familial (first-degree) | 27                     | 27              | Passive viewing          | Implicit               | Faces   | Negative stimuli > neutral stimuli <sup>a</sup>                  |
| van der Velde <i>et al.</i> , 2015 (34) | CHR                     | 15                     | 16              | Emotion regulation       | Explicit               | IAPS (complex scenes of people)                       | Negative stimuli > neutral stimuli                               |
| Wang <i>et al.</i> , 2018 (30)          | Psychometric            | 34                     | 30              | Emotion recognition      | Explicit               | Faces   | Fearful stimuli > neutral stimuli                                |
| Wolf <i>et al.</i> , 2011 (59)          | Familial (first-degree) | 20                     | 25              | Emotion recognition      | Explicit               | Faces   | Negative stimuli > neutral stimuli <sup>a</sup>                  |
| Wolf <i>et al.</i> , 2015 (32)          | CHR                     | 260                    | 220             | Emotion recognition      | Explicit               | Faces   | Fearful stimuli > neutral stimuli <sup>a</sup>                   |

CHR, clinical high risk; HC, healthy control subjects; IAPS, International Affective Picture System.

<sup>a</sup>The included contrast was not the one originally reported in the article but a new generated one.

<sup>b</sup>Note that we included one study with a contrast involving positively valenced stimuli. Nevertheless, around 70% of the stimuli represented negative emotions. We therefore considered this study as largely representing negative emotions and we refer to the general contrast included in this meta-analysis as a negative emotional stimuli vs. nonemotional stimuli contrast.

<sup>c</sup>This number corresponds to the dataset sent by the authors which is slightly different from the dataset reported in the paper. This is because the authors retrieved the latest available dataset.

<sup>d</sup>The recruitment of participants for this unpublished study started in February 2012 and ended in June 2016.

### Study Characteristics

The included studies encompassed 2 types of tasks: 1) implicit tasks, which used emotional stimuli while using instructions with a nonemotional focus (e.g., passive viewing of emotional images, age, or gender recognition), and 2) explicit tasks, in which instructions specifically require to focus on the emotional component of the stimuli (e.g., emotion recognition, emotion regulation, emotion evaluation, rating of emotional arousal, matching of emotional faces). Details regarding the task design and included contrasts for each study are reported in Table 1. Further details (mean age, percentage of male participants, field strength) are reported in Table S2. Following recommendations from the latest version of SDM, we only included a single contrast per study (see Supplemental Methods for selection criteria).

### Analyses

We ran an image-based meta-analysis using statistically unthresholded T-maps provided by authors. This approach is more sensitive than the more common coordinate-based meta-analyses (50,51), because it accounts for effect sizes and is also sensitive to moderate subthreshold effects that are consistent across studies (52).

For the sake of homogeneity, some of the included contrasts were not those reported in the original articles, but instead new contrasts generated by the authors at our request based on their methodological design (Table 1).

**Whole-Brain Frequentist Analyses.** Frequentist meta-analyses were performed using the latest version of SDM based on permutation of subject images (SDM-PSI, version 6.21) (53). Traditional meta-analysis methods (e.g., activation likelihood estimation and multilevel kernel density analysis) test for spatial convergence, evaluating in each voxel whether studies found activation more often in one group than in another. In contrast, SDM-PSI uses a new algorithm that tests whether activation in each voxel is significantly different between groups (53). This approach has been argued to be more robust and has several advantages: the interpretation of results is more straightforward and is not based on spatial assumptions that could be violated, and voxel-level significance is independent of the distribution of activation across the brain. Moreover, this method accounts for both activations and deactivations, allowing opposite findings to potentially cancel each other. Finally, the method uses a threshold-free cluster enhancement (TFCE) approach to address the multiple comparison issue, which, compared with other thresholding techniques, has the benefit of not defining an arbitrary cluster-forming threshold (54).

We included contrasts broadly depicting a comparison between the perception of negative emotional stimuli and nonemotional stimuli (i.e., neutral stimuli, control condition, or implicit baseline). We initially examined these contrasts separately in at-risk individuals and healthy control subjects (within-group meta-analysis). Of the 17 studies included in the meta-analysis, 1 study could not provide within-group T-maps and therefore was excluded from this analysis (55). Thus, the within-group meta-analysis included 16 studies, cumulating 619 at-risk individuals and 711 healthy control

subjects. Then, the same contrasts were examined in at-risk individuals versus healthy control subjects (between-group meta-analysis). In total, 17 studies were included in this analysis for a total of 677 at-risk individuals versus 805 healthy control subjects.

Results were corrected for multiple comparisons across the whole brain using a TFCE-corrected threshold of  $p_{TFCE} < .05$ .

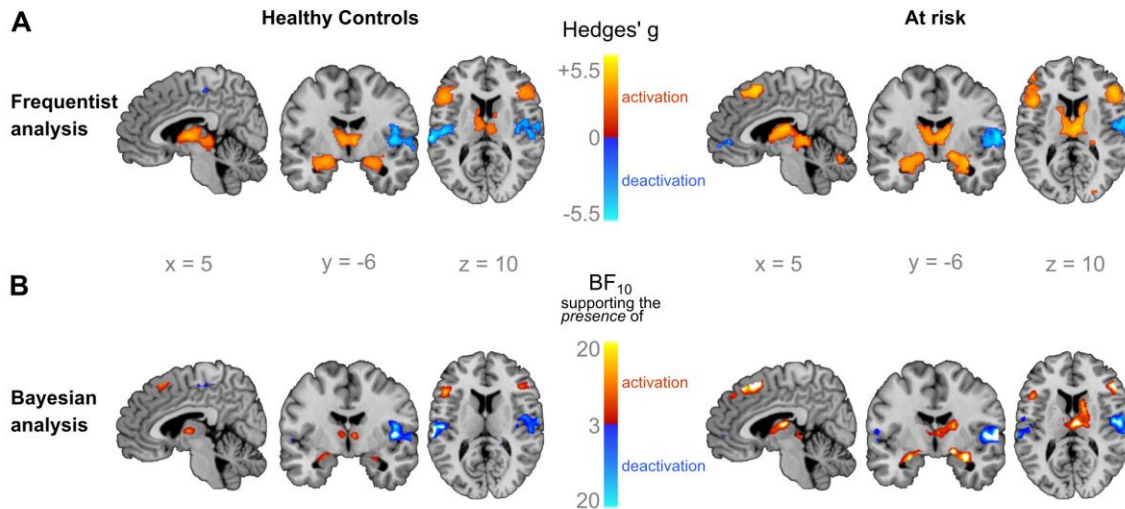
**Whole-Brain Bayesian Analyses.** Bayesian analyses were performed with the BayesFactorFMRI (56,57) toolbox to quantify evidence in favor of the null and alternative hypotheses. This toolbox uses R and Python code to perform Bayesian voxelwise meta-analysis of T-maps. The output is a meta-analytic map storing a Bayes factor (BF) for each voxel. The BF is the ratio of the likelihood of the data under the alternative hypothesis ( $H_1$ , hypothesizing a meaningful effect in a within- or between-group analysis) and the likelihood of the same data under the null hypothesis ( $H_0$ , hypothesizing the absence of a meaningful effect in a within- or between-group analysis).  $BF_{10}$  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 a BF between 10 and 30 represents strong evidence (58). Results are thus reported at a threshold of  $BF > 3$ .

The BayesFactorFMRI toolbox only computes BFs in voxels that are covered by all included studies (similar to second-level analyses performed in SPM or FSL). Therefore, 1 study with partial brain coverage (59) (see Supplemental Methods) had to be excluded from these analyses to retain information in a substantial part of the brain covered by all the remaining studies. The approach was similar to the initial frequentist analyses; we first performed within-group analyses ( $n = 15$  studies), examining the negative emotional versus nonemotional contrast in at-risk individuals ( $n = 599$ ) and healthy control subjects ( $n = 686$ ) before performing the between-group analyses ( $n = 16$  studies) in at-risk individuals ( $n = 657$ ) versus healthy control subjects ( $n = 780$ ).

**ROI Analyses (Frequentist and Bayesian).** Given the key role of the amygdala in emotion processing, and previous findings in patients with schizophrenia (6–11), the bilateral amygdala was selected for ROI-based analyses. The amygdala was anatomically defined using the Melbourne Subcortex Atlas (60).

Averaged effect sizes and associated variances were extracted separately for the left and right amygdala for each study using SDM-PSI. These values were used to perform frequentist and Bayesian meta-analyses as well as to generate forest plots and contour-enhanced funnel plots.

Frequentist ROI meta-analyses were performed using SDM-PSI. Bayesian ROI meta-analyses were performed using R (version 4.1.2) by fitting a random-effect Bayesian model [using the *brms* package (61)], and defining weakly informative priors for the mean (normal distribution centered at 0 with a variance of 1) and variance (Half-Cauchy distribution with peak at 0 and scaling parameter of 0.5) of the pooled true effect as suggested by Harrer *et al.* (62).



**Figure 1.** Within-group meta-analyses of negative emotion processing. Brain regions showing activation (in red) and deactivation (in blue) during negative emotion processing as revealed by frequentist (A) and Bayesian (B) analyses for healthy control subjects and at-risk individuals. Regions typically involved in emotion processing were activated (e.g., bilateral amygdala, thalamus, inferior frontal gyrus). Note that results were consistent across statistical approaches and that the patterns of activation and deactivation were remarkably similar in healthy control subjects and at-risk individuals. Functional maps are overlaid on the Colin 27 anatomical template. Frequentist analyses are thresholded at  $p_{TFCE} < .05$  and Bayesian analyses are thresholded at  $BF_{10} > 3$ . BF, Bayes factor; TFCE, threshold-free cluster enhancement.

**RESULTS**

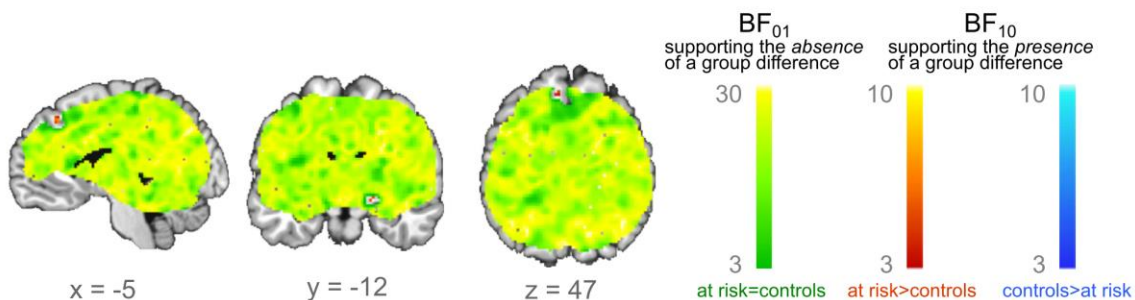
Whole-brain maps of within- and between-group meta-analyses are available on NeuroVault (52) for both frequentist and Bayesian analyses (<https://neurovault.org/collections/CRLVUOUJ/>).

**Whole-Brain Frequentist Analyses**

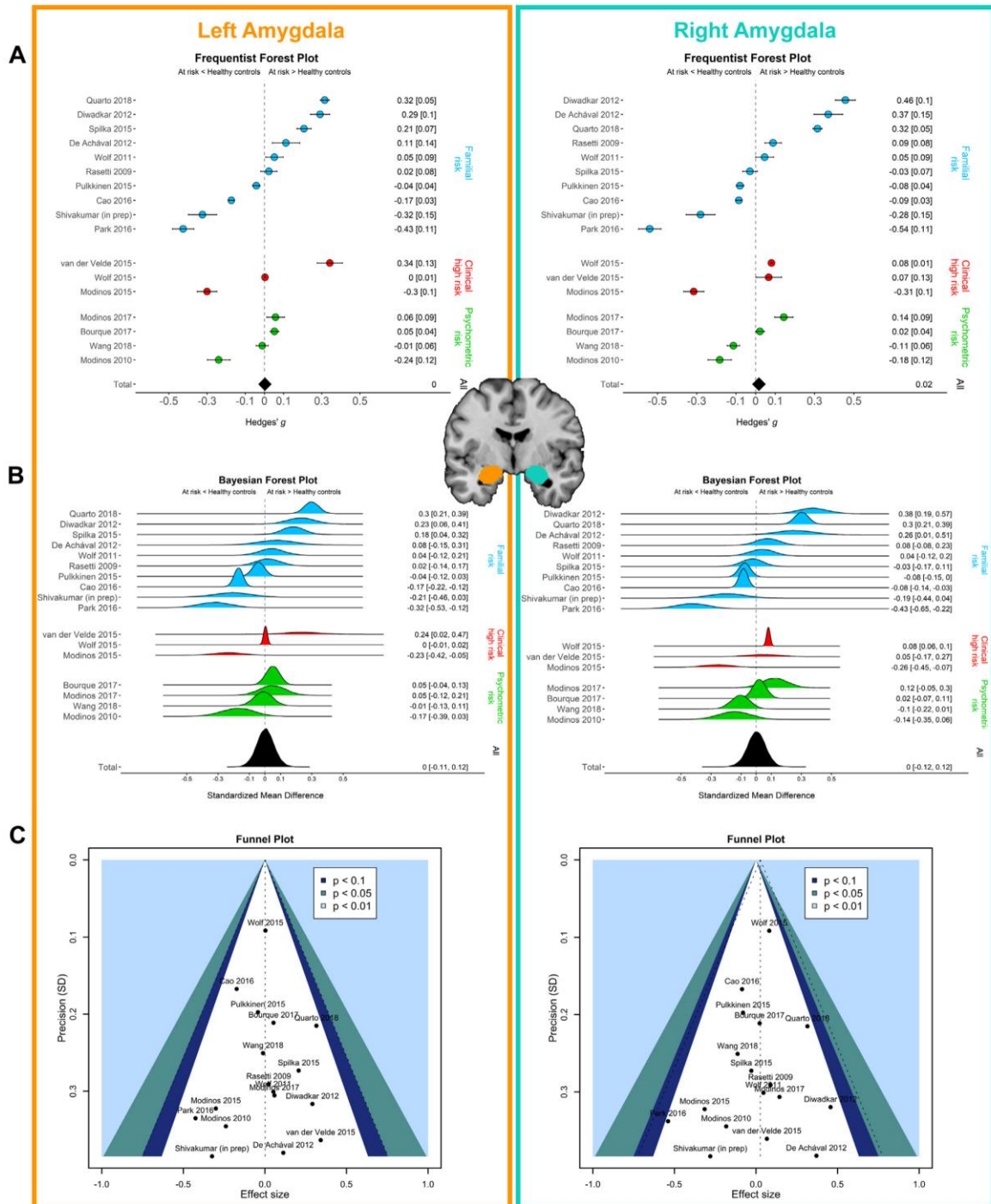
Across included studies ( $n = 16$ ), the meta-analyses of within-group T-maps in healthy control subjects and in at-risk

individuals revealed significant activations in several brain regions typically involved in emotion processing, such as the bilateral amygdala, thalamus, and inferior frontal gyrus (Figure 1A; see Table S3 for Montreal Neurological Institute [MNI] coordinates). The pattern of activation and deactivation was remarkably similar between healthy control subjects and at-risk individuals.

The whole-brain between-group meta-analysis ( $n = 17$  studies) revealed no significant group differences at  $p_{TFCE} < .05$ .



**Figure 2.** Between-group Bayesian meta-analysis of negative emotion processing. Voxels with moderate evidence supporting hyperactivation in at-risk individuals compared with healthy control subjects are depicted in red ( $BF_{10} > 3$ ). Voxels with at least moderate evidence supporting a hypoactivation in at-risk individuals compared with healthy control subjects are depicted in blue ( $BF_{10} > 3$ ). Voxels with at least moderate (or higher) evidence supporting the absence of differences in at-risk individuals compared with healthy control subjects are depicted in green ( $BF_{01} > 3$ ). Only 2 small clusters showed moderate evidence (i.e.,  $3 < BF_{10} < 10$ ) in favor of hyperactivation in at-risk individuals compared with healthy control subjects. In contrast, strong evidence (i.e., most  $BF_{01} > 10$ ) in favor of the absence of group differences was found almost across the whole brain. Functional maps are overlaid on the Colin 27 anatomical template. Results are thresholded at  $BF > 3$ . BF, Bayes factor.



### Whole-Brain Bayesian Analyses

Results of within-group Bayesian meta-analyses ( $n = 15$  studies) largely reproduced the activation pattern revealed by frequentist analyses, showing activation in the bilateral amygdala, thalamus, and inferior frontal gyrus (Figure 1B).

The between-group Bayesian meta-analysis ( $n = 16$  studies) revealed 2 small clusters showing moderate evidence in favor of increased activation in at-risk individuals compared with healthy control subjects. These clusters were observed in the left superior frontal gyrus ( $x = -6, y = 34, z = 46, BF_{10} = 4.78$ , voxel size = 10) and the right perihippocampal white matter ( $x = 20, y = -12, z = -10, BF_{10} = 7$ , voxel size = 6) (see Figure 2 in red). No region showed evidence in favor of a decreased activation in at-risk individuals compared with healthy control subjects (see Figure 2 in blue). Instead, evidence in favor of the absence of differences in brain activation in at-risk individuals compared with healthy control subjects was found across almost the entire brain, with  $BF_{01}$  reaching values up to 30, indicating strong evidence in favor of  $H_0$  (see Figure 2 in green).

### ROI Analyses (Frequentist and Bayesian)

Frequentist meta-analysis in amygdala ROIs revealed no significant group differences in either the left ( $g = 0.00, p = .52$ ) or the right ( $g = 0.02, p = .58$ ) hemisphere (Figure 3A).

Bayesian meta-analysis found strong evidence for the absence of group differences between at-risk individuals and healthy control subjects in the left (standardized mean difference = 0; 95% CI,  $-0.11$  to  $-0.12$ ;  $BF_{01} = 18.2$ ) and the right (standardized mean difference = 0; 95% CI,  $-0.12$  to  $-0.12$ ;  $BF_{01} = 17.31$ ) amygdala (Figure 3B).

### Heterogeneity, Publication Bias, and Robustness

In additional sensitivity analyses (see Supplemental Methods for details), we found that results did not differ according to the definition of 1) type of risk for schizophrenia (i.e., familial risk, CHR, or psychometric risk), 2) type of contrast (i.e., negative emotional stimuli vs. neutral stimuli or vs. control condition/implicit baseline), 3) type of task (i.e., implicit or explicit), or 4) type of emotional stimuli (i.e., when restricting analyses to those studies only including faces). We also show that our data have low heterogeneity (Figure S2) and showed no obvious sign of publication bias (Figure 3C), and that the results were not driven by outlier studies.

### DISCUSSION

Our meta-analysis aimed to investigate whether brain activation in response to negative emotional stimuli could be considered as an endophenotype of schizophrenia. Results showed that healthy control subjects and individuals at risk of

schizophrenia present a remarkably similar pattern of brain activation in response to processing negative emotional stimuli. These similarities were observed in salient regions of the emotion processing network including the amygdala, thalamus, and inferior frontal gyrus. In line with this observation, the between-group meta-analysis did not reveal group differences. Notably, not only did the frequentist meta-analysis fail to reveal significant differences between healthy control subjects and at-risk individuals, but the Bayesian meta-analysis provided strong support (i.e.,  $BF_{01} > 10$ ) for the absence of such group differences across the entire brain. Two small clusters showed hyperactivation in at-risk individuals, but these were located in regions irrelevant to the process at stake, were only observed in Bayesian analyses, and were associated with only moderate evidence (i.e.,  $BF_{10} < 10$ ). We thus prefer to refrain from speculating about these results, which do not appear to be robust. Finally, ROI analyses specifically focusing on the amygdala confirmed the absence of between-group activation differences. This null result is particularly notable because the amygdala plays a primary role in emotion processing and has shown blunted responses in patients with schizophrenia in multiple meta-analyses (6–11). Given the combination of frequentist and Bayesian approaches and the careful curation of the included datasets, we believe that our results are particularly strong and reliable. The inescapable inference is that in at-risk individuals, brain responses to negative emotional stimuli are too variable to be considered as a reliable endophenotype of schizophrenia. This observation is consistent with a previous meta-analysis of brain responses to emotional stimuli in CHR individuals (37), which did not find any differences with healthy control subjects.

Our strategy has the merit of bringing together several definitions that are commonly used to identify at-risk individuals (i.e., familial, CHR, psychometric), exploring the vulnerability spectrum of schizophrenia. Yet, these different definitions of risk (based on genetic vulnerability, subthreshold clinical symptoms, or high schizotypy traits) as well as differences in transition rates (63–65) may increase heterogeneity and consequently mask subtle but reliable group differences. To identify potential variability across definitions, we therefore conducted separate subgroup analyses (see Supplemental Methods). None of these analyses revealed significant results. Nevertheless, it is important to emphasize that some diagnostic uncertainty and heterogeneity still remain within each subgroup. This clinical variability introduces some additional variance that may diminish our ability to observe more subtle group differences. The use of mega-analytic methods employing subject-level data is a promising development to address this issue (51). Also, moving away from categorical to more dimensional definitions of mental health conditions

**Figure 3.** Region of interest (ROI) meta-analyses of negative emotion processing. Graphical representations of values extracted from left and right amygdala. (A) Frequentist forest plot depicting the mean  $\pm$  variance of effect sizes for group comparison. The black diamond represents the overall effect size. (B) Bayesian forest plot depicting Bayesian estimates of the true effect size and posterior distribution of each study for group comparison. Posterior distribution depicted in black represents the Bayesian meta-estimate and posterior distribution of the overall effect size. Note that for both Bayesian and frequentist forest plots, distinguishing subgroups as a function of the definition of at risk did not seem to affect the results. (C) Contour-enhanced funnel plot: the dotted part depicts the overall effect size and 95% confidence interval around this overall effect size, while the colored areas represent different levels of statistical significance ( $p < .1, p < .05$ , and  $p < .01$ , corresponding to 90%, 95%, and 99% CI, respectively, around an effect size of 0) (75). Symmetrical funnel plots for both the left and right amygdala suggest no evidence for publication bias, which is further strengthened by all studies lying in the area of statistical non-significance ( $p > .1$ ).

should allow to better take into account this variability by improving the granularity of nosological descriptions.

Moreover, while this meta-analysis focuses on emotion perception, emotion processing consists of multiple components such as experience, regulation, and expression. Examined individually, such components may be able to show robust association with schizophrenia vulnerability, allowing for refined candidate endophenotypes. For instance, there are some evidence of brain abnormalities in emotion regulation in patients with schizophrenia (46,66), which are also reported in at-risk individuals (34,67).

Finally, it should be noted that the amygdala, a key region in emotion processing, is particularly sensitive to susceptibility artifacts, leading to blood oxygen level-dependent signal dropout. As a result, some of the included studies had only partial coverage of the amygdala. This observation calls for optimized acquisition protocols in future studies to circumvent this issue (see [Supplemental Methods](#) for a more detailed discussion).

Despite these limitations, we believe that the cutting-edge methodology of our meta-analysis provides strong empirical support for the results. First, we performed an image-based meta-analysis, which considers effect sizes from individual voxels across the entire brain as opposed to coordinate-based meta-analyses (such as activation likelihood estimation and multilevel kernel density analysis) that rely only on peak localization (50,51). This difference bestows our approach with increased sensitivity. Second, we contacted authors of selected studies and solicited originally collected data with specific contrasts based on their methodological design. It is notable that in addition to maximizing homogeneity across studies, this strategy is less susceptible to publication bias; indeed, both positive and negative results are collected, and studies reporting only ROI analyses are not systematically excluded, thus eliminating a potential bias (68). Third, we performed both within- and between-group analyses. In addition to confirming the activation of regions involved in emotion processing, the within-group meta-analyses revealed similar brain activation patterns in healthy control subjects and at-risk individuals. This similarity provides a straightforward and logical explanation for the absence of group differences in the between-group meta-analyses. Fourth, the Bayesian approach reproduced the results of the frequentist analyses, even when it was not subject to the typical limitations of the latter. Such convergence provides quantitative evidence in favor of the null hypothesis (69). Finally, this meta-analysis follows the recently updated PRISMA guidelines (39), ensuring the greatest level of transparency (70).

In conclusion, this meta-analysis reveals that individuals at risk of schizophrenia do not show clear abnormalities in brain activation during negative emotion perception. This finding has both clinical and theoretical implications for schizophrenia. In general, it is unclear whether emotional deficits are involved in schizophrenia etiopathogenesis and therefore are present before the onset of the illness or should be considered as a consequence of the disease itself (for instance, due to chronic effects of the disease, medication treatment, or physiological adaptation secondary to the illness). While it is well established that brain responses to emotions are blunted in patients with schizophrenia, investigating these responses in at-risk

individuals brings us a step closer to elucidating their role, helping to differentiate cause from consequence. In this meta-analysis, we reported an absence of group differences between at-risk individuals and healthy control subjects. This suggests that blunted brain responses to emotions are more likely to represent a consequence of the illness, i.e., a state marker that manifests itself only when the illness is active. Following this reasoning, abnormal brain responses to emotions are unlikely to be a useful endophenotype with the potential to help clinicians detect individuals at risk of schizophrenia.

It should also be noted that the endophenotype reasoning posits a continuum between the genetic risk and the expression of the abnormal trait. Yet, recent literature confirms that schizophrenia risk hinges on the interaction between genetic and environmental factors (71). Thus, the nonappearance of abnormal brain responses to emotions observed here in at-risk individuals could be explained by the absence, in the medical history of these subjects, of the environmental conditions necessary to reveal the phenotype variation.

Recent work has proposed that the blunted limbic responses observed in patients with schizophrenia during emotion processing could be at least partially explained by enhanced reactivity to neutral stimuli (12). Based on this observation, one might speculate that the neurotypical brain responses found in at-risk individuals might reflect a downward normalization of brain responses toward neutral stimuli, and not just an upward normalization of brain responses to emotional stimuli.

Crucially though, it should be emphasized that emotions are processed by a system of distributed and interconnected brain structures and that functional connectivity during emotion processing has been shown to be impaired in schizophrenia (72,73). A few studies investigating brain connectivity during emotion processing have also reported differences in individuals with familial risk (26,55,74), CHR (43), and psychometric risk (67) compared with healthy control subjects, mostly showing a blunted connectivity between limbic and frontal regions. In the framework of a chronic and poor-outcome disorder such as schizophrenia, endophenotypes are considered essential to help clinicians identify subjects at risk of schizophrenia and inform preventive approaches. Results of the present meta-analysis may prove useful to guide future research, and we suggest that future studies focus on the role of disrupted corticolimbic coupling among at-risk individuals as a potential candidate endophenotype of schizophrenia.

#### ACKNOWLEDGMENTS AND DISCLOSURES

AMF was supported by the Fondation Pierre Deniker. EF was supported by the Fondation de France. GS was supported by the Agence Nationale de la Recherche (Grant No. ANR-19-CE37-0012-01) and the Fondation NRJ-Institut de France.

The funding source had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

AMF and GS have full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: AMF, GS, and EF. Acquisition (sharing data and/or performing additional analyses): all authors but AMF, GS, and EF. Analyses and interpretation of data: AMF, GS, and EF. Statistical analyses: AMF, GS,



and EF. Drafting of the manuscript: AMF, GS, and EF. Critical revision of the manuscript for important intellectual content: all authors. Obtained funding: EF. Authors who were exclusively involved in data acquisition and critical revision of the manuscript are listed following alphabetical order in the authorship list.

We thank Hyemin Han, Educational Psychology Program, University of Alabama, Tuscaloosa, AL, for his help with the BayesFactorFMRI toolbox.

A previous version of this article was published as a preprint on bioRxiv: <https://doi.org/10.1101/2022.05.31.22275506>.

GB has received lecture fees from Lundbeck. EF has received consultancy fees from Bristol Myers Squibb, Janssen-Cilag, Lilly, Lundbeck, Otsuka Pharmaceutical Co., Ltd., Recordati, and Sanofi and has lectured for AbbVie, AstraZeneca, Bristol Myers Squibb, Janssen-Cilag, Lundbeck, Otsuka, MSD, and Sanofi. AM-L has received grants from the Federal Ministry of Education and Research; the German Research Foundation; the Seventh Framework Programme of the European Union and the Ministry of Science, Research, Australia; and the Arts of the State of Baden-Württemberg. All other authors report no biomedical financial interest or potential conflicts of interest.

## ARTICLE INFORMATION

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Received Mar 8, 2022; revised and accepted Jun 7, 2022.

Supplementary material cited in this article is available online at <https://doi.org/10.1016/j.biopsych.2022.06.013>.

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## CHAPITRE II - Peut-on utiliser les stimuli neutres comme un bon comparateur pour étudier le traitement émotionnel ?

### *[Article #2]*

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Dans la schizophrénie, il y a également un intérêt accru pour le traitement des **visages dits neutres**, c'est-à-dire qui ne sont pas en train d'exprimer des émotions spécifiques.

Cet intérêt s'inscrit dans le cadre de l'hypothèse de la « **saillance aberrante** », qui postule que les patients atteints de schizophrénie ont tendance à attribuer une signification motivationnelle à des stimuli considérés comme non pertinents par des sujets sans troubles psychiatriques. Il a été proposé que les symptômes positifs résulteraient de cette attribution aberrante de la saillance, et les idées délirantes émergeraient d'une tentative cognitive d'organiser ces expériences de saillance aberrante (Potvin et al., 2016). Selon certains auteurs, la dopamine striatale élevée jouerait un rôle clé dans la transformation d'un stimulus externe neutre en une entité attrayante ou aversive, et pourrait amener les patients à attribuer une émotion et un sens à des événements normalement insignifiants (Kapur, 2003).

Déjà en 2012, Anticevic et collaborateurs ont montré dans une méta-analyse que chez les patients vivant avec une schizophrénie il y a une réduction de l'activité de l'amygdale seulement dans les études qui utilisent un contraste du type [émotions négatives versus stimuli neutres], alors que ce résultat n'est pas retrouvé dans les études qui comparent les patients et les sujets contrôles directement sur la condition émotionnelle (Anticevic et al., 2012). Ils ont donc suggéré que les études utilisant des stimuli neutres comme référence pour étudier la composante émotionnelle pourraient avoir confondu une activation accrue aux stimuli neutres avec une sous-activation dans la condition émotionnelle d'intérêt.

Les résultats de cette méta-analyse ont indirectement soulevé la possibilité que les patients atteints de schizophrénie pourraient présenter des hyperactivations en réponse à des stimuli neutres, expliquant (au moins partiellement) les hypoactivations limbiques aux stimuli émotionnels souvent rapportées. En d'autres mots, Anticevic et collaborateurs ont proposé que les patients vivant avec une schizophrénie auraient une activation de l'amygdale « normale » en réponse à des stimuli négatifs, et accrue en réponse à des stimuli neutres.

Toutefois, en 2012 Anticevic et collaborateurs n'ont pas pu directement étudier les réponses cérébrales aux stimuli neutres pour prouver cela, car peu d'études rapportaient cette analyse. Depuis, il y a eu un intérêt accru vers l'activation cérébrale en réponse aux stimuli neutres, et en 2019 Dugré et collaborateurs ont réalisé une méta-analyse incluant 23 études qui ont comparé des stimuli neutre à une croix de fixation chez des patients vivant avec une schizophrénie par rapport à des sujets contrôles (Dugré et al., 2019). Ils ont pu montrer que les **patients vivant avec une schizophrénie** présentaient bien une **activation accrue envers les stimuli neutres** dans plusieurs régions limbiques telles que l'amygdale, l'hippocampe, le parahippocampe, le putamen et l'insula. Ces hyperactivations limbiques étaient particulièrement prononcées lors de la présentation de visages neutres. Les auteurs ont conclu que ces résultats étaient en accord avec le modèle de la saillance aberrante, selon lequel les délires émergent d'un effort cognitif top-down de la part du patient pour donner un sens à des expériences perçues comme étant anormalement saillantes. Ces auteurs ont suggéré que les études futures devraient explorer les corrélats cérébraux chez les individus à risque de développer une schizophrénie, car les études actuellement disponibles rapportent des résultats plutôt hétérogènes. Face à cette variabilité, ils suggèrent également de définir avec précision les critères pour identifier la population à risque d'intérêt (Dugré et al., 2020).

Ainsi, dans une deuxième étude, nous avons étudié l'**activité cérébrale vers les visages neutres** chez des apparentés de premier degré de patients vivant avec une schizophrénie, en utilisant une **approche méta-analytique** ([Article #2](#), Fiorito et al., *Schizophr*, 2024).

Nous avons utilisé le logiciel Seed-based d Mapping, en intégrant des cartes statistiques de l'ensemble du cerveau provenant de cinq études, ainsi que des coordonnées issues de deux études. Nous avons cumulé un total de **157 apparentés de premier degré et 207 sujets contrôles**. Nous avons d'abord examiné séparément les réponses cérébrales aux stimuli émotionnels chez les personnes à risque et les sujets contrôles (analyse intra-groupe), puis chez les personnes à risque versus les sujets contrôles (analyse inter-groupe).

La méta-analyse intra-groupe a montré des activations robustes dans plusieurs régions impliquées dans le traitement des visages neutres, telles qu'un réseau postérieur, qui comprend des zones impliquées dans le traitement visuel des visages comme le gyrus fusiforme, ainsi que l'amygdale. Chez les apparentés, ces activations n'ont pas atteint un

niveau de significativité statistique, suggérant une activation moindre de ces zones. Ce résultat a été confirmé par la méta-analyse inter-groupe, qui a révélé une **diminution de l'activation chez les apparentés**, en particulier dans les régions du système limbique tel que l'amygdale.

Cela suggère que, chez les individus à risque génétique de schizophrénie, les mécanismes de traitement des visages neutres sont altérés, en particulier dans les régions limbiques impliquées dans le traitement émotionnel. De façon intéressante, ce pattern de diminution de l'activation cérébrale contraste avec celui observé chez les patients atteints de schizophrénie, qui montre une augmentation des activations dans les régions limbiques, suggérant ainsi la possible présence de **facteurs protecteurs**. L'identification des facteurs protecteurs, tout comme celle de facteurs à risque, pourraient aider les cliniciens à mieux prédire la transition vers la psychose et à informer les cibles thérapeutiques pour la prévention. Par ailleurs, nos résultats suggèrent de porter une **attention particulière à l'utilisation des visages neutres comme condition de comparaison dans les études en IRMf**. Ce biais a déjà été observé chez les patients atteints de schizophrénie (Dugré et al., 2019), et nous étendons cette mise en garde aux apparentés de premier degré, qui pourraient également présenter des réponses atypiques face à ces stimuli. En effet, vu que les visages neutres peuvent provoquer des réponses cérébrales variées chez les patients vivant avec une schizophrénie, leur apparentés et des sujets contrôles, cela pourrait fausser les résultats lorsqu'on s'intéresse à la composante émotionnelle.

#### Article #2

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

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*Schizophrenia*, 10, 38 (2024). <https://doi.org/10.1038/s41537-024-00452-6>

## Résumé graphique Article #2



# BLUNTED RESPONSES TO NEUTRAL FACES IN HEALTHY FIRST-DEGREE RELATIVES OF PATIENTS WITH SCHIZOPHRENIA: An image-based fMRI meta-analysis

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### BACKGROUND



Behaviour:

- Patients with **schizophrenia** misattribute emotional significance to **neutral faces**
- **Inconsistent findings** have been reported in **healthy first-degree relatives**

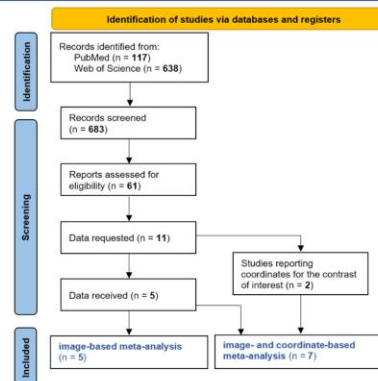


Cerebral correlates:

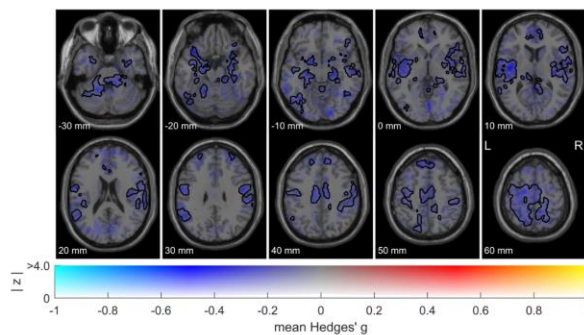
- Behavioral deficits observed in patients are associated with **hyperactivations** of the limbic system (e.g., amygdala)
- Do healthy **first-degree relatives** exhibit abnormal **brain responses to neutral faces?**

### METHODS

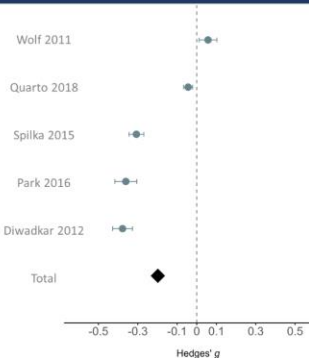
- **Combined image- and coordinate-based meta-analysis** (with both coordinates and unthresholded T-maps as input)
- Pubmed, Web of Science
- **Neutral vs control condition/baseline** contrast
- **207 healthy controls, 157 first-degree relatives**
- **SDM-PSI for whole-brain analyses**
- **Sensitivity** analyses



### RESULTS



- **Decreased activations** in relatives compared with healthy controls in **limbic areas**
- **Sensitivity analyses** showing **no influence of age or quality** of the study; **low heterogeneity** across most of the brain



- **Forrest plot** showing reduced activation in right amygdala (similar pattern in left amygdala)

### CONCLUSIONS

- Limited research on neutral face processing; **future studies** should prioritize this area
- Hypoactivations in relatives contrast with hyperactivations in patients, suggesting a potential **protective factor**
- **Caution** advised when using neutral faces as a baseline control in **fMRI studies**

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

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Schizophrenia is characterized by the misattribution of emotional significance to neutral faces, accompanied by overactivations of the limbic system. To understand the disorder's genetic and environmental contributors, investigating healthy first-degree relatives is crucial. However, inconsistent findings exist regarding their ability to recognize neutral faces, with limited research exploring the cerebral correlates of neutral face processing in this population. Thus, we here investigated brain responses to neutral face processing in healthy first-degree relatives through an image-based meta-analysis of functional magnetic resonance imaging studies. We included unthresholded group-level T-maps from 5 studies comprising a total of 120 first-degree relatives and 150 healthy controls. In sensitivity analyses, we ran a combined image- and coordinate-based meta-analysis including 7 studies (157 first-degree relatives, 207 healthy controls) aiming at testing the robustness of the results in a larger sample of studies. Our findings revealed a pattern of decreased brain responses to neutral faces in relatives compared with healthy controls, particularly in limbic areas such as the bilateral amygdala, hippocampus, and insula. The same pattern was observed in sensitivity analyses. These results contrast with the overactivations observed in patients, potentially suggesting that this trait could serve as a protective factor in healthy relatives. However, further research is necessary to test this hypothesis.

*Schizophrenia* (2024)10:38; <https://doi.org/10.1038/s41537-024-00452-6>

### INTRODUCTION

Schizophrenia is a debilitating psychiatric disorder affecting approximately 1% of the population. According to the aberrant salience hypothesis<sup>1</sup>, patients with schizophrenia tend to attribute motivational significance to stimuli that are considered as irrelevant by healthy subjects. Consistent with this theory, patients with schizophrenia exhibit heightened subjective arousal in response to emotionally neutral stimuli including faces, scenes, words, sounds<sup>2</sup>. Notably, studies have reported that patients misattribute emotional significance to neutral faces, and tend to perceive such faces as negatively valenced<sup>3–5</sup>. This biased interpretation of faces, a central element of our social environment, significantly impacts patients' social skills and overall functioning<sup>6</sup>.

At the brain level, a recent functional magnetic resonance imaging (fMRI) meta-analysis by Dugré and colleagues<sup>7</sup> examined the processing of emotionally neutral stimuli in schizophrenia. Compared with healthy controls, patients with schizophrenia showed increased activation in limbic regions in response to neutral stimuli, in particular when processing neutral faces. This finding supports the idea that patients do not perceive emotionally neutral faces as being devoid of emotional significance.

Although substantial progress has been made in understanding the processing of emotionally neutral stimuli in schizophrenia, there is a dearth of research examining this phenomenon in healthy first-degree relatives of patients with schizophrenia. Indeed, these individuals share on average 50% of their genes with their siblings diagnosed with schizophrenia and are considered to be at familial risk. Since many of these genes are involved in brain development, genetic variations are likely to impact brain structure and ultimately brain function. It is thus to be expected that common genetic heritability may manifest at the neuroimaging level<sup>8–10</sup>. Studies focusing on first-degree relatives are thus crucial, as they are unaffected by potential confounding factors (such as chronic effects of the disease, medication treatment, or physiological adaptation secondary to the illness) which are inextricably tied to schizophrenia itself, thus limiting our understanding of the cerebral correlates of this chronic illness.

Some previous work in first-degree relatives has reported a tendency to over-attribute negative emotions to neutral faces, in line with the behavioral bias observed in patients<sup>11,12</sup>. However, these findings have not been replicated in more recent studies with larger sample sizes or confirmed by meta-analyses<sup>13–16</sup>. To date, neuroimaging studies have mainly focused on the general processing of emotional faces, with recent meta-analytical work showing that brain activity patterns in individuals at enhanced risk

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are similar to healthy controls<sup>17</sup>. Only a few studies have investigated the neural mechanisms associated with the processing of neutral faces in first-degree relatives. This scarcity of studies arises partly from the challenges inherent to conducting research within this population. As a consequence, the few studies that have tackled this question have typically relied on relatively modest sample sizes, hence providing limited statistical power<sup>18,19</sup>. In this context, the main objective of our study was to rely on a meta-analytical approach to consolidate the results from small sample studies that have investigated brain responses to neutral faces in healthy first-degree relatives. We aimed to identify potential brain differences with healthy controls, eventually advocating for further exploration and investigation within this domain in forthcoming research.

Due to the scarcity of studies investigating this question, we systematically reviewed all task-based fMRI studies that used neutral faces as stimuli, regardless of whether activations to neutral faces were specifically investigated or even reported in the original article. Authors were contacted and asked to provide whole-brain maps showing 1) brain responses towards neutral faces as compared to a control condition separately in first-degree relatives and healthy controls (which were used to perform within-group meta-analyses), 2) brain responses towards neutral faces as compared with a control condition in first-degree relatives versus healthy controls (which were used to perform between-group meta-analyses).

## MATERIALS AND METHODS

This meta-analysis was conducted following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA<sup>20</sup>), using an approach similar to our recent work<sup>17</sup>. The protocol for this meta-analysis was not pre-registered. We conducted a comprehensive literature search using PubMed and Web of Science, identifying records published until August 22nd, 2023. The search used a combination of terms constructed according to 4 stems relating to (a) schizophrenia (schizophren\*, psychosis), (b) first-degree relatives (relatives, first-degree, siblings, twins, brothers, sisters, offspring, parents, genetic risk) (c) neuroimaging (neuroimaging, functional magnetic resonance imaging, fMRI), and (d) face processing (emotion\*, affect, mood, face, facial) (see Supplementary Methods for the exact combination of keywords employed in the search strategy). Additionally, we performed a reference list inspection of the included studies to identify articles that were not identified through the database search.

### Inclusion and exclusion criteria

Inclusion criteria were the following: studies that (a) were written in English; (b) reported a comparison between healthy first-degree relatives and healthy controls; (c) used task-based fMRI with face processing, and (d) used neutral faces.

It should be noted that this meta-analysis specifically focused on faces as neutral stimuli in order to increase homogeneity among the included contrasts and acknowledge the significant social importance associated with these stimuli, especially in light of previous findings in patients<sup>7</sup>. Here we conceptualized neutral face processing as the collective neural processes engaged in perceiving, recognizing, and interpreting faces without any salient visual features, and thereby assumed to lack emotional significance.

The following exclusion criteria were applied: studies that (a) did not report a neutral face versus control condition/baseline contrast, or for which the authors could not provide the contrast when queried; (b) did not use visual stimuli of faces in their protocol; (c) did not use original samples of individuals (i.e., used same data as other included study); (d) could only provide a

general F-statistic instead of direct comparisons between groups; (e) were published conference papers, and (f) were systematic reviews or meta-analyses.

It should be noted that we systematically searched for studies whose methodology was *capable* of investigating neutral face processing, regardless of whether they actually reported the analysis of interest in the original article. This approach was adopted to maximize the pool of potentially eligible studies.

### Included studies

The literature search yielded 683 unique papers (see Fig. 1). Initial screening based on title and abstract was performed by AMF. After these exclusions, 61 full articles were independently screened to be assessed for eligibility by AMF and GS. Disagreements were resolved through discussion and mediation by a third author (EF). The application of inclusion and exclusion criteria filtered the analysis to a total of 11 papers (see Supplementary Methods for details on study exclusion). The corresponding authors of these papers were contacted to obtain unthresholded group-level T-maps, associated with within- and between-groups effects. Following this correspondence, we received data from 5 studies that were included in the image-based meta-analysis.

Among the studies for which we could not retrieve data, 2 reported the peak coordinates of the contrast of interest and were thus included in a sensitivity analysis combining these coordinate-based results with the aforementioned image-based results (i.e., 7 studies in total). We were unable to include data from the remaining studies<sup>21–24</sup> due to various reasons, including no reported peak coordinates for the contrast of interest, non-responsive corresponding authors (after multiple reminders), and unavailable or lost data. Furthermore, since these studies did not report results regarding brain responses to neutral faces, they could not be included in a more comprehensive qualitative analysis such as a systematic review. We thus exclusively relied on the rigor of a more quantitative meta-analytical approach, which further ensures a principled weighing of individual studies.

The quality of included studies was assessed (by AMF) using a modified version of the quality assessment checklist employed in previous neuroimaging meta-analysis<sup>25</sup> (see Table S1).

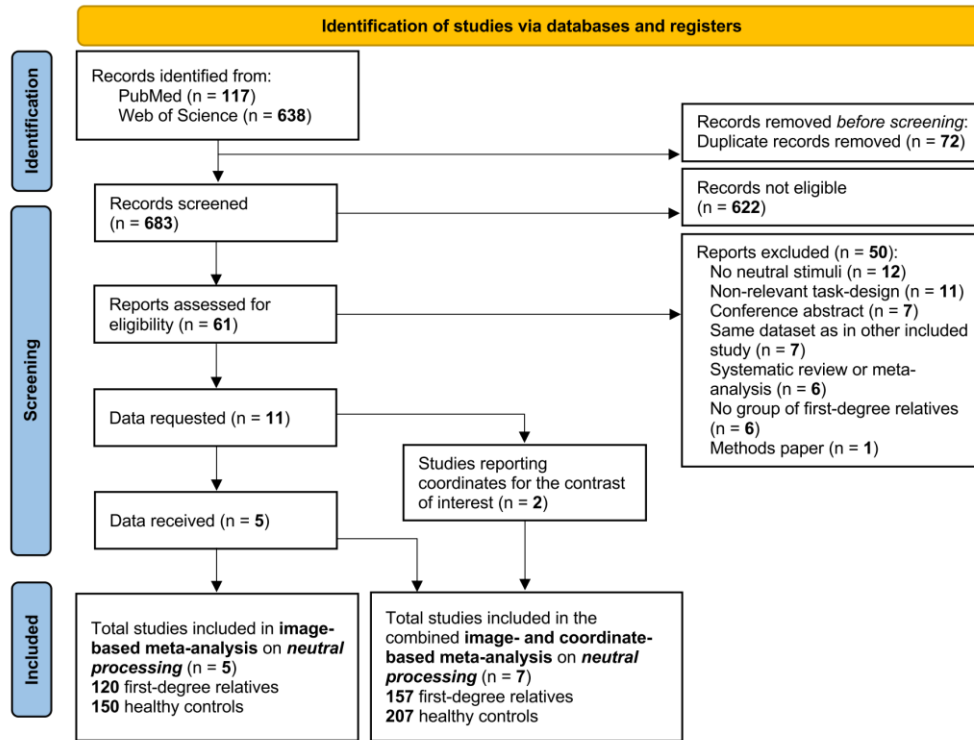
It should be noted that one of the included studies had a partial coverage of the brain<sup>26</sup>. There is a common consensus regarding the need to exclude studies employing region-of-interest analyses, to avoid biasing whole-brain results in favor of these regions. However, the brain coverage of this study was much wider than classical ROIs and encompassed all the brain regions typically involved in face processing.

Details regarding the task design, demographic variables, and included contrasts are reported in Table 1. The main objective, main results, and quality score of the included studies are reported in Table S2.

### Analyses

Using statistically unthresholded T-maps provided by the authors, we performed an image-based meta-analysis, which is more sensitive compared with more common coordinate-based meta-analyses<sup>27,28</sup>. This method accounts for effect sizes and is also sensitive to moderate subthreshold effects that are consistent across studies<sup>29</sup>. Such an approach is particularly critical in healthy first-degree relatives who are expected to exhibit more subtle brain differences compared to those found in patients with schizophrenia.

Some of the included contrasts were not reported in the original articles but were generated by the authors upon our request (see Table 1). This was necessary since several of the eligible studies included neutral faces only as a comparator for other conditions, without reporting brain responses to these stimuli in the original article.



**Fig. 1 Flow chart.** This diagram depicts the selection procedure of studies.

**Whole-brain analyses.** Meta-analyses were performed using Seed-based d-mapping software based on permutation of subject images (SDM-PSI<sup>30</sup>, version 6.21). Traditional meta-analysis methods (e.g., Activation Likelihood Estimation, ALE, and Multilevel Kernel Density Analysis, MKDA) test for spatial convergence, evaluating in each voxel whether studies found activation more often in one group compared with another. In contrast, the SDM-PSI algorithm is regarded as more precise, as it tests for significant differences in activation between groups in each voxel<sup>30</sup>. Rather than convergence, this approach considers the consistency of activation or deactivation patterns across studies, providing a more robust assessment of common neural substrates. Even with a limited number of studies, consistent effects are more likely to be detected. Furthermore, it is possible to employ the SDM-PSI algorithm to conduct meta-analyses using whole-brain unthresholded T-maps, yielding a substantial gain in statistical power and sensitivity compared with coordinate-based meta-analyses<sup>27,28</sup>. Accordingly, the validation process of the SDM-PSI algorithm has indicated that a 100% sensitivity in detecting the proportion of activated voxels can be achieved by using the T-maps from at least three studies<sup>30</sup>.

Furthermore, the SDM-PSI approach offers several advantages, including a more straightforward interpretation of results, independence of voxel-level significance from the distribution of activation across the brain, and the ability to account for both activations and deactivations. Finally, this method employs a threshold-free cluster enhancement (TFCE) approach to address the multiple comparison issue, which compared with other thresholding techniques has the benefit of not defining an arbitrary cluster-forming threshold<sup>31</sup>.

We included a single contrast per study depicting a comparison between the perception of neutral faces versus a control condition or interstimulus interval (e.g., fixation cross, checkerboard pattern).

We initially examined these contrasts separately in first-degree relatives and healthy controls (within-group meta-analysis). Then, the same contrasts were examined in first-degree relatives versus healthy controls (between-group meta-analysis). A total of 120 first-degree relatives and 150 healthy controls from five studies were included in these analyses.

Results were corrected for multiple comparisons across the whole brain using a TFCE-corrected threshold of  $p_{TFCE} < 0.05$ .

**Sensitivity and heterogeneity analyses.** To assess the robustness of our findings, we conducted sensitivity analyses using a combined image- and coordinate-based meta-analysis. Specifically, through multiple imputations the SDM algorithm reconstructs estimated 3D statistical maps from coordinates<sup>27,30</sup> (see Supplementary Methods for a description of this procedure). This process allows for the combination of statistical parametric maps, significantly enhancing sensitivity but less often available, with peak coordinates, more commonly reported in original articles.

In addition to the five studies that were included in our original analysis, we could include two additional studies that reported peak coordinates in their original articles ( $n = 7$  studies), cumulating 157 first-degree relatives and 207 healthy controls.

Furthermore, in order to verify that our results were not partially driven by the inclusion of one study with partial brain coverage<sup>26</sup>, we ran an additional analysis excluding this study ( $n = 4$  studies).

Additionally, to account for the potential variance that could be attributed to age and study quality, we conducted a supplementary analysis, including mean age and total quality score (as assessed by the quality assessment checklist, see Table S1; total quality score is reported in Table S2) as covariates in our model.

Finally, we examined the whole-brain heterogeneity map generated by SDM-PSI. This map contains a  $I^2$  statistic for each voxel, which represents the percentage of total variation in effect

**Table 1.** Included studies investigating brain activation in response to neutral faces.

| Reference                     | Kinship   | Number of participants            | Age mean (SD)                        | Male sex; No (%)             | Field strength | Task used                    | Contrast included                             | T-maps/Coordinates |
|-------------------------------|---|-----------------------------------|--------------------------------------|------------------------------|----------------|------------------------------|---|--------------------|
| Diwadkar et al. <sup>42</sup> | First-degree relatives (offspring)                    | REL (17);<br>HC (25) <sup>a</sup> | REL: 14.3 (3.1);<br>HC: 14.6 (2.6)   | REL: 12 (63);<br>HC: 16 (67) | 4 T            | Emotion recognition (n-back) | Neutral > Control Condition                   | T-maps             |
| Oertel et al. <sup>43</sup>   | First-degree relatives                                | REL (23);<br>HC (27)              | REL: 43.6 (14.3);<br>HC: 34.2 (11.4) | REL: 5 (22);<br>HC: 13 (48)  | 3 T            | Associative memory           | Neutral > Interstimulus Interval              | Coordinates        |
| Park et al. <sup>44</sup>     | First-degree relatives (siblings or offspring)        | REL (20);<br>HC (17)              | REL: 23.9 (5.6);<br>HC: 23.06 (3.9)  | REL: 7 (35);<br>HC: 8 (47)   | 3 T            | Gender recognition           | Neutral > Interstimulus Interval              | T-maps             |
| Pirnia et al. <sup>45</sup>   | First-degree relatives                                | REL (14);<br>HC (30)              | REL: 39.6 (11.8);<br>HC: 29.3 (9.0)  | REL: 5 (36);<br>HC: 24 (80)  | 3 T            | Associative memory           | Neutral > Interstimulus Interval              | Coordinates        |
| Quarto et al. <sup>34</sup>   | First-degree relatives (siblings)                     | REL (36);<br>HC (56)              | REL: 35.4 (10.1);<br>HC: 31.4 (10.4) | REL: 13 (36);<br>HC: 30 (54) | 3 T            | Gender recognition           | Neutral > Interstimulus Interval <sup>b</sup> | T-maps             |
| Spilka et al. <sup>35</sup>   | First-degree relatives (parents, siblings, offspring) | REL (27);<br>HC (27)              | REL: 41.2 (15.5);<br>HC: 40.7 (11.1) | REL: 10 (37);<br>HC: 13 (48) | 3 T            | Passive viewing              | Neutral > Control Condition                   | T-maps             |
| Wolf et al. <sup>26</sup>     | First-degree relatives (parents and siblings)         | REL (20);<br>HC (25)              | REL: 42.3 (14.8);<br>HC: 39.0 (10.7) | REL: 9 (45);<br>HC: 12 (48)  | 3 T            | Emotion recognition          | Neutral > Interstimulus Interval <sup>b</sup> | T-maps             |

SD standard deviation, HC healthy controls, REL healthy first-degree relatives, T Tesla.

<sup>a</sup>This number corresponds to the dataset sent by the authors which is slightly different from the dataset reported in the paper. This is because the authors retrieved the latest available dataset.

<sup>b</sup>The included contrast was not the one originally reported in the article but a newly generated one.

size due to between-study heterogeneity rather than sampling error.

## RESULTS

Whole-brain maps of within- and between-group meta-analyses as well as whole-brain maps of sensitivity analyses are available on NeuroVault [<https://neurovault.org/collections/13917/>].

### Whole-brain within-group meta-analysis

In healthy controls, the meta-analysis of within-group T-maps revealed significant activations in several brain regions of the limbic system, such as bilateral amygdala and insula, as well as bilateral putamen and fusiform face area. Deactivations were observed in regions of the default mode network, such as bilateral posterior cingulate gyrus, superior parietal gyrus, occipital lobe, and pre-subgenual frontal cortex (Fig. 2A, see Table S3 for MNI coordinates).

In healthy first-degree relatives, no statistically significant brain activations were observed. However, it is worth noting that activations in the fusiform face area and amygdala were detected, although they did not reach the threshold for statistical significance. In contrast, relatives showed numerous significant deactivations, in the bilateral superior temporal gyrus, middle inferior temporal gyrus, precentral and postcentral gyrus, subgenual frontal cortex, and parahippocampal gyrus (Fig. 2B, see Table S3 for MNI coordinates).

### Whole brain between-group meta-analysis

First-degree relatives showed significantly decreased activations compared with healthy controls during the processing of neutral faces, particularly in limbic areas including the bilateral amygdala, hippocampus, and insula (Fig. 3, see Table S4 for MNI coordinates). Remarkably, among these regions, the amygdala was the only one showing a clear bilateral hypoactivation pattern, i.e., was significantly activated in healthy controls while not significantly activated in first-degree relatives. No increased activations were observed.

In forest plots, we have depicted the effect sizes of individual studies included in the present meta-analysis both for the left and right amygdala, which were defined independently as anatomical regions of interest using the Melbourne Subcortex Atlas<sup>32</sup>. The pattern of results is very similar in the left and right amygdala, reducing the chances of a false positive result (see Fig. S1). Furthermore, publication bias was assessed in the left and right amygdala, first through visual inspection of the funnel plot, which represents the 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 Fig. S2 for a 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 the left ( $t = -0.28$ ,  $p = 0.7996$ ) or right ( $t = -1.32$ ,  $p = 0.277$ ) amygdala, indicating reasonable symmetry of the funnel plot and thus no evidence of a publication bias.

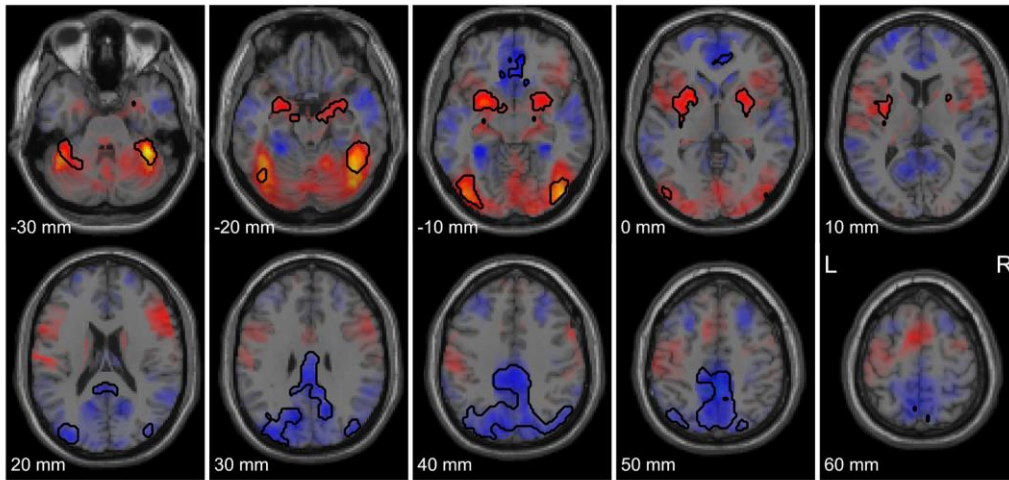
### Sensitivity and heterogeneity analyses

The results of the combined image- and coordinate-based meta-analysis largely replicated the findings of the main analysis (see Fig. S3).

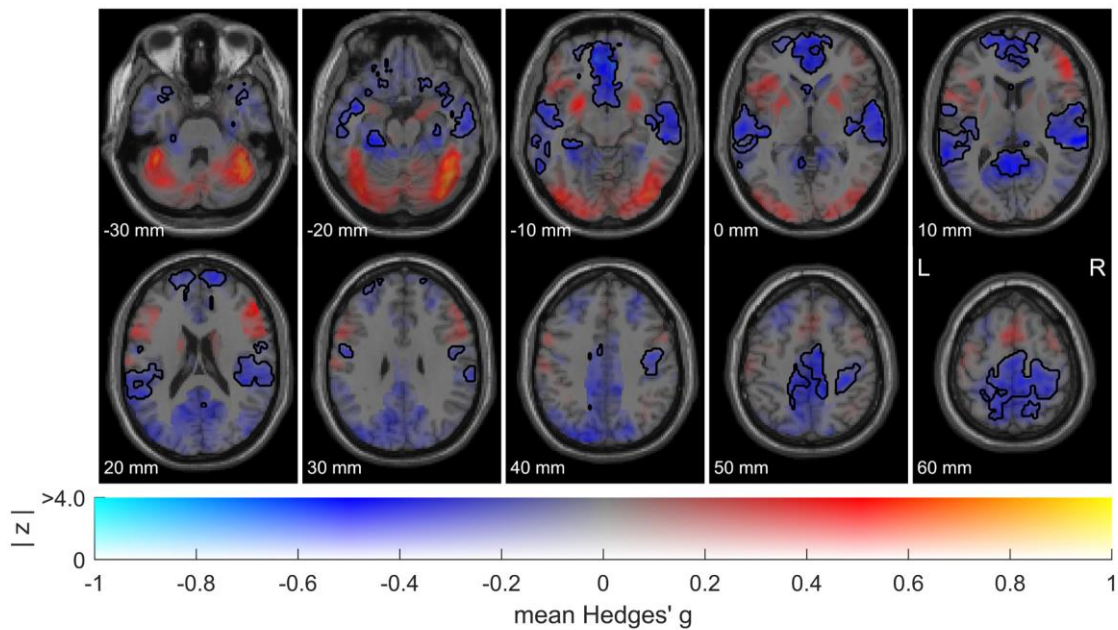
Moreover, when excluding the study with partial brain coverage as well as when running the main analysis by adding mean age and study quality as covariates, the main results remained similar (see Figs. S4 and S5).

Despite low heterogeneity observed across most of the brain as indicated by the heterogeneity map, we identified some clusters exhibiting substantial heterogeneity (see Fig. S6).

### A. Healthy controls



### B. First-degree relatives



**Fig. 2 Image-based within-group meta-analysis.** Combining functional neuroimaging studies investigating brain responses to neutral faces in healthy controls ( $n = 5$  studies; 150 healthy controls) (A) and healthy first-degree relatives of patients with schizophrenia ( $n = 5$  studies; 120 first-degree relatives) (B). These are dual-coded images<sup>46,47</sup> 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 a threshold of  $p_{\text{TFC}} < 0.05$ .

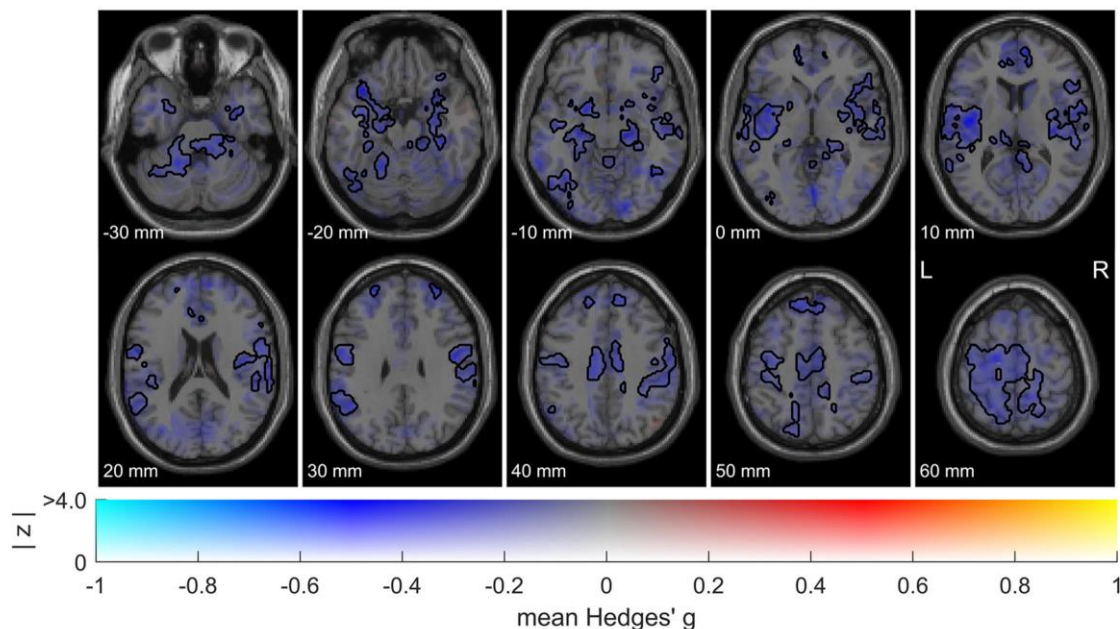
However, these clusters were mostly non-overlapping with the peak of (de-)activations observed in the between-group comparison.

#### DISCUSSION

In this image-based meta-analysis, we compared brain responses to neutral faces between healthy first-degree relatives of patients with schizophrenia and healthy controls.

It is now well-established that neutral face processing in physiological conditions involves not only activation of the posterior network (which includes the visual and fusiform face areas), but also of other core structures such as the amygdala<sup>33</sup>. The within-group meta-analysis showed robust activations in these regions in healthy controls, whereas in first-degree relatives these activations did not reach statistical significance, suggesting that these areas are activated to a lesser extent. This result was confirmed in the between-group meta-analysis, which revealed

## First-degree relatives &gt; Healthy controls



**Fig. 3 Image-based between-group meta-analysis.** Combining 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<sup>46,47</sup> 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 a threshold of  $p_{TFCE} < 0.05$ .

significant hypoactivation of the amygdala and limbic regions in first-degree relatives compared with healthy controls. Notably, included studies did not report a difference in performance on the behavioral task between first-degree relatives and healthy controls (besides one study that found decreased accuracy specifically for identification of sad faces<sup>26</sup>). This finding challenges the possibility that the observed differences could be attributed to a lack of engagement or involvement in the task by first-degree relatives.

Our findings are particularly noteworthy in light of previous studies in patients with schizophrenia, indicating both misattribution of emotional valence to neutral faces<sup>3-5</sup> and emotional brain hypersensitivity to emotionally neutral stimuli<sup>7</sup> (although this result in patients could not be replicated in the present meta-analysis, as only 2 out of 5 studies included both first-degree relatives and patients with schizophrenia<sup>34,35</sup>). Given prevailing work reporting no abnormalities in recognition of neutral faces in healthy first-degree relatives<sup>13-16</sup> and given the crucial role of the amygdala and limbic regions in the attribution of emotional and motivational significance, the observed decrease of activation in these regions in healthy first-degree relatives may represent a physiological protective marker against the onset of schizophrenia disorder. Indeed, it should be noted that only a minority of first-degree relatives undergo the development of schizophrenia (i.e., transition rate of 13% at 1-year follow-up<sup>36</sup>). Furthermore, the majority of individual studies included in this meta-analysis have focused on first-degree relatives who passed the median age of onset for schizophrenia (i.e., 25 years<sup>37</sup>) and are thus less susceptible to developing schizophrenia. Accordingly, while healthy first-degree relatives share about half of their genes with their affected sibling, other genetic factors, possibly related to

their remaining genetic heritage, may have protective potential against polygenic schizophrenia-associated variants. The search for risk markers of schizophrenia has so far largely overlooked the search for protective factors<sup>38</sup>. Yet, both have the potential to help clinicians better predict the transition to psychosis and inform therapeutic targets for prevention. Indeed, recent research has shown a growing interest in these genetic factors, leading to a shift in focus from a polygenic risk score to what is defined as a "polygenic resilience score" for schizophrenia<sup>39</sup>.

Consistent with our findings, recent research has outlined a cerebral circuit underpinning protective factors against the established adversities of mental illnesses such as schizophrenia, within which the capacity to downregulate the amygdala constitutes a key mechanism<sup>40</sup>. In line with his idea, recent studies employing real-time fMRI neurofeedback of the amygdala have demonstrated that training the downregulation of amygdala activity facilitates emotion regulation<sup>41</sup>. This ability to regulate emotions aids in coping with emotionally challenging situations and, consequently, mitigating stress -an influential factor in the onset of schizophrenia. Interestingly, previous studies investigating brain connectivity in response to neutral face processing in offspring of patients with schizophrenia have reported increased cortico-limbic top-down modulation<sup>42</sup>.

The correlation suggested between reduced engagement of the limbic system and reduced vulnerability to schizophrenia warrants further exploration. Particularly, future longitudinal studies are imperative to investigate whether decreased activation of limbic regions is specific to individuals at familial risk who do not transition to schizophrenia. This exploration is pivotal in discerning the genuine protective role of this trait, which might hold promise

as a potential predictive factor for prognosis. A critical initial step towards elucidating this point involves clarifying the relationship between limbic responses and schizophrenia symptomatology. Prior studies have suggested that heightened limbic activation in individuals with schizophrenia may contribute to positive symptoms, particularly paranoid or delusional ideation, but failed to provide empirical evidence supporting this relationship<sup>7</sup>. Elucidating this link may help in discerning whether the present finding of diminished limbic activation in first-degree relatives represents a protective factor, potentially explaining an absence of symptomatology in these relatives.

These results should be considered in light of several limitations. First, we could only include a limited number of studies ( $n = 7$ , among which 5 unthresholded T-maps). This is mainly due to the limited availability of fMRI studies exploring neutral processing in first-degree relatives. Indeed, merely 5 studies have reported such an analysis in their original publication (see Table 1). Yet, none of these studies primarily focused on examining brain activity related to neutral stimuli (see Table S2 for an overview of the main objective and results of the included studies). In this context, our approach consisted of contacting the corresponding authors of all the studies that employ neutral faces in their task design, regardless of whether activations to neutral faces were reported in the original article. This procedure allowed us to collect results from 2 additional studies. Furthermore, although the number of included studies was limited, the use of unthresholded T-maps significantly increases accuracy, as compared with meta-analysis relying on peak coordinates. Finally, it has been shown that using SDM-PSI, a 100% sensitivity in detecting the proportion of activated voxels can be reached by using at least the T-maps from 3 studies<sup>30</sup>. Second, it is important to emphasize that schizophrenia is a highly heterogeneous disorder and that this heterogeneity poses a substantial challenge to our understanding. This variability is not only evident among patients but is equally pronounced among healthy relatives. Our meta-analysis, while providing valuable insights, must be interpreted in light of this inherent heterogeneity. It also underscores the need for future studies to delve deeper into the intricacies of clinical variations within both patient and familial populations. Third, one of the included studies has a partial coverage of the brain<sup>26</sup>. However, we largely replicated the results of the main analysis while excluding this study (see Fig. S4). Moreover, since SDM-PSI software does not test for spatial convergence, but rather for significant differences in activation, the inclusion of studies with partial brain coverage does not lead to an increase of false positive results.

## CONCLUSION

Despite these limitations, this study constitutes the first attempt to meta-analytically investigate the brain processing of neutral faces in healthy first-degree relatives of patients with schizophrenia. Compared with healthy controls, we have reported widespread decreased activations in first-degree relatives, particularly in regions of the limbic system. This pattern of decreased activations contrasts with the one observed in patients with schizophrenia, showing increased activations of limbic regions<sup>7</sup>, and possibly suggesting the presence of protective factors. The findings of this meta-analysis warrant and encourage future investigations into the brain responses to neutral stimuli among first-degree relatives, a facet of research that has been significantly overlooked. Furthermore, our results align with those of Dugré and colleagues<sup>7</sup> in cautioning against the use of neutral faces as a baseline control condition in future fMRI studies and extend this vigilance to populations of first-degree relatives. Indeed, neutral faces may elicit different brain responses in these various populations of subjects and may confound results.

## DATA AVAILABILITY

Whole-brain maps of within- and between-group meta-analyses as well as whole-brain maps of sensitivity analyses are available on NeuroVault [<https://neurovault.org/collections/13917/>].

Received: 15 October 2023; Accepted: 16 February 2024;

Published online: 19 March 2024

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## ACKNOWLEDGEMENTS

A.M.F. was supported by the Fondation Pierre Deniker. E.F. was supported by the Fondation de France. G.S. was supported by the Agence Nationale de la Recherche (Grant number ANR-19-CE37-0012-01) and the Fondation NRJ-Institut de France. The funding source had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

## AUTHOR CONTRIBUTIONS

A.M.F. has full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: A.M.F., G.S. and E.F. Acquisition (sharing data and/or performing additional analyses): G.B., A.C., V.A.D., V.M.G., R.C.G., J.S.K., T.Q., M.J.S., D.H.W., J.-Y.Y. Analyses and interpretation of data: A.M.F., G.S. and E.F. Statistical analyses: A.M.F., G.S. and E.F. Drafting of the manuscript: A.M.F., G.S. and E.F. Critical revision of the manuscript for important intellectual content: A.M.F., G.B., J.B., A.C., V.A.D., V.M.G., R.C.G., J.S.K., T.Q., B.R., M.J.S., D.H.W., J.-Y.Y., E.F., G.S. Obtained funding: E.F. Authors who were exclusively involved in data acquisition and/or critical revision of the manuscript are listed following alphabetical order in the authorship list.

## COMPETING INTERESTS

G.B. has received lecture fees from Lundbeck. E.F. has received consultancy fees from Bristol Myers Squibb, Janssen-Cilag, Lilly, Lundbeck, Otsuka Pharmaceutical Co., Ltd., Recordati, and Sanofi and has lectured for AbbVie, AstraZeneca, Bristol Myers Squibb, Janssen-Cilag, Lundbeck, Otsuka, MSD, and Sanofi. M.J.S. is a full-time employee of Winterlight Labs. All other authors report no biomedical financial interest or potential conflicts of interest.

## ADDITIONAL INFORMATION

**Supplementary information** The online version contains supplementary material available at <https://doi.org/10.1038/s41537-024-00452-6>.

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### CHAPITRE III - Peut-on considérer la connectivité cérébrale en réponse à des stimuli émotionnels comme un endophénotype de la schizophrénie ?

#### [Article #3]

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Dans le chapitre précédent, nous avons observé que le traitement des **visages neutres** active les régions du système limbique de manière distincte chez les apparentés de premier degré des patients atteints de schizophrénie, comparativement aux sujets contrôles (*Article #2, Fiorito et al., Schizophr, 2024*). Ce constat est en accord avec les études rapportant des différences d'activation cérébrale entre les patients et les sujets contrôles, ce qui soulève **des réserves quant à l'utilisation de ces stimuli en tant que comparateurs dans les études en IRMf**. Toutefois, la majorité des études portant sur la perception émotionnelle utilisent des stimuli neutres comme référence, contribuant ainsi à l'hétérogénéité des résultats observés. Les méta-analyses, qui synthétisent les données existantes, se sont donc principalement, voire exclusivement, focalisées sur des études comparant des stimuli émotionnels à des stimuli neutres (Anticevic et al., 2012; Delvecchio et al., 2013; Dong et al., 2018; Fiorito et al., 2022; Taylor et al., 2012). Cette approche limite la compréhension globale des corrélats cérébraux associés à ces déficits.

Dans le Chapitre I, nous avons montré, à travers une approche méta-analytique, que les activations cérébrales aux stimuli émotionnels ne semblent pas montrer des preuves solides pour être considérés comme un endophénotype de la schizophrénie (*Article #1, Fiorito et al., Biol Psychiatry, 2022*). A travers une revue systématique de la littérature, nous avons répertorié toutes les études qui avaient utilisé l'IRMf lors d'une tâche émotionnelle. Ainsi, nous avons essentiellement inclus des études qui rapportaient un contraste du type [émotionnel versus neutre]. Nous avons inclus trois groupes à risque de développer une schizophrénie : les apparentés de patients, les individus à risque clinique, et ceux présentant des traits de schizotypie élevés. Nos analyses ont montré des preuves en faveur de l'absence de différences significatives entre ces groupes. Si l'inclusion de plusieurs types de risque permet de généraliser nos résultats, elle introduit également de l'hétérogénéité dans les conclusions. Ainsi, nous avons également réalisé des analyses de sensibilité, montrant que nos résultats ne changeaient pas lorsque nous considérons uniquement les études portant sur un



type de population spécifique ou utilisant un contraste particulier (stimuli émotionnels versus stimuli neutres ou versus une condition contrôle). Cependant, en réduisant le nombre d'études dans chaque sous-analyse, la puissance statistique diminue. De plus, une partie de l'hétérogénéité persiste, ce qui représente une limitation intrinsèque des méta-analyses.

Nous avons également émis l'hypothèse que les **déficits émotionnels** observés au niveau comportemental, tant chez les patients que chez leurs apparentés (Gao et al., 2021; Martin et al., 2020), pourraient être **sous-tendus par des anomalies dans la communication** entre les régions impliquées dans le traitement émotionnel. En effet, peu d'études ont jusqu'à présent examiné la connectivité cérébrale lors du traitement émotionnel chez les apparentés de patients.

Ainsi, nous avons conduit une étude en **IRMf chez 37 patients vivant avec une schizophrénie, 39 apparentés de premier degré (frères ou sœurs des patients), et 42 sujets contrôles** (*Article #3, Fiorito et al., In Prep*). Nous avons utilisé une tâche émotionnelle écologique, intégrant des visages émotionnels dans des contextes également émotionnels. Nous nous sommes intéressés aux visages exprimant des émotions négatives, qui ont été comparés à une **condition contrôle soigneusement appariée**. Après avoir évalué la performance des participants, nous avons réalisé des analyses d'activation en utilisant des approches fréquentistes et bayésiennes. Nous avons également examiné la **connectivité** cérébrale de l'amygdale via une analyse d'interaction psychophysologique.

Au niveau comportemental, nous avons observé la tendance endophénotypique typiquement décrite dans la littérature. En ce qui concerne l'activation cérébrale, les **apparentés présentaient une hypoactivation** par rapport aux sujets contrôles dans un cluster de l'hémisphère droit, incluant le **gyrus temporal supérieur**, une région très impliquée dans la physiopathologie de la schizophrénie, **et le cortex somatosensoriel**. Grâce aux analyses bayésiennes, nous avons également démontré que les patients présentaient des anomalies d'activation dans le cortex somatosensoriel droit, suggérant un possible rôle **endophénotypique**. Nous avons montré une **absence de différences d'activation entre les patients et leurs apparentés par rapport aux sujets contrôles dans la plupart des voxels du cerveau, y compris l'amygdale**. Ce constat est en accord avec notre travail précédent (Fiorito et al., 2022), mais diffère des résultats des méta-analyses menées chez les patients, où des

hypoactivations envers les stimuli émotionnels sont souvent rapportées, principalement en comparaison à des stimuli neutres (Anticevic et al., 2012; Delvecchio et al., 2013; Dong et al., 2018; Fiorito et al., 2022; Taylor et al., 2012). Comme suggéré précédemment, ces hypoactivations dans les régions limbiques pourraient avoir été surestimées à cause de l'utilisation de stimuli neutres comme référence (Anticevic et al., 2012; Dugré et al., 2019). En adoptant comme condition de référence une condition contrôle plutôt que des stimuli neutres, nous avons proposé que les déficits d'activation cérébrale en réponse aux stimuli émotionnels soient plutôt liés à un dysfonctionnement des régions responsables du traitement émotionnel de haut niveau, permettant la simulation des états affectifs via une représentation somatosensorielle.

Concernant la connectivité cérébrale, nous avons montré que chez les **apparentés** par rapport aux sujets contrôles, lors du traitement des visages négatifs **l'amygdale droite était plus fortement connectée au cuneus droit** que lors de la condition contrôle. Nous avons proposé que ce résultat puisse refléter un mécanisme compensatoire mis en place chez les apparentés, facilitant l'intégration et l'interprétation émotionnelle à travers le renforcement de l'interaction entre les circuits émotionnels et visuels.

Ces résultats ouvrent de nouvelles pistes dans notre compréhension des corrélats cérébraux du traitement émotionnel dans le continuum de la schizophrénie.

### Article #3

Emotional perception in schizophrenia: insights from brain activation and connectivity among patients, siblings, and healthy controls

Anna M. Fiorito, Hyemin Han, Guillaume Sescousse\*, Eric Fakra\*

*In Preparation [preliminary results]*

## Résumé graphique Article #3



# EMOTIONAL PERCEPTION IN SCHIZOPHRENIA: INSIGHTS FROM BRAIN ACTIVATION AND CONNECTIVITY AMONG PATIENTS, SIBLINGS, AND HEALTHY CONTROLS

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## BACKGROUND

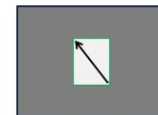
- **Emotion face perception** is impaired in patients with schizophrenia and, to a lesser extent, in **their healthy relatives**
- Thus, these deficits may serve as a potential **endophenotype** of schizophrenia
- However, **brain correlates** of emotion perception in schizophrenia are **unclear** due to:
  1. Use of **neutral stimuli** as comparators of emotional stimuli in fMRI studies *despite different brain responses in patients, relatives, and healthy controls*
  2. Limited studies on **brain connectivity** *despite the involvement of interconnected regions in emotion processing*



## METHODS



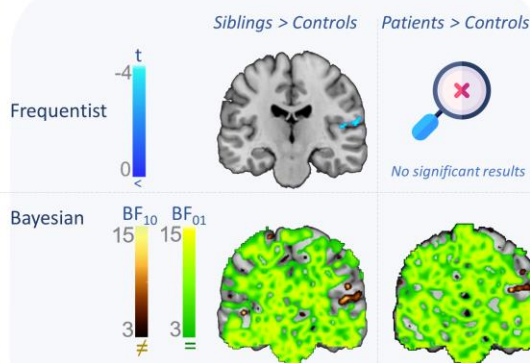
- **fMRI** study with **37** patients with schizophrenia, **39** siblings, **42** healthy controls
- **Activation** analysis using a well-matched control condition (i.e. arrows direction)
- **Negative Faces vs Control Condition** contrast
- One-way **ANOVA** with **posthoc t-tests**
- Complementary approach based on frequentist (SPM12) and Bayesian (BayesFactorFMRI) statistics
- Generalized psychophysiological interaction (**gPPI**) analyses with left/right amygdala as seeds



## RESULTS

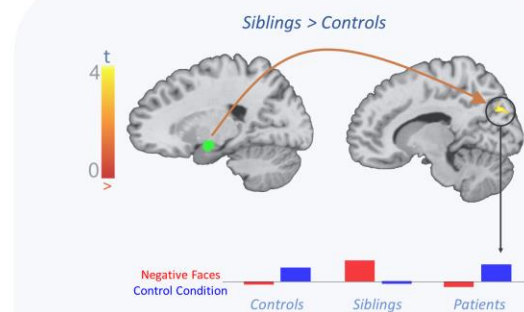
### Behavioral analyses

#### Activation analyses



- **Common pattern of decreased activations** in right somatosensory cortex in siblings and patients

#### Connectivity analyses



- **Increased connectivity** between right amygdala and right cuneus in siblings

## CONCLUSIONS

- Possible **endophenotypic pattern** in the activation of the right somatosensory cortex
- **Normal activity** in limbic regions, such as the **amygdala**, previously implicated in emotional impairments in schizophrenia
- **Abnormal connectivity** in siblings, possibly reflecting a compensatory mechanism

## Title

### **Emotional perception in schizophrenia: insights from brain activation and connectivity among patients, siblings, and healthy controls**

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## Abstract

**Introduction:** Facial emotion recognition has been proposed as a potential endophenotype for schizophrenia, as both patients with schizophrenia and their healthy relatives show difficulties in recognizing negative facial emotions. In psychiatric disorders, brain functioning is considered highly informative for endophenotype research. However, recent studies have raised questions about our current understanding of the neural correlates of emotion recognition across the schizophrenia spectrum, pointing out two major limitations in previous research. First, individual fMRI studies and meta-analyses have predominantly used neutral stimuli as a comparator in emotional tasks. Yet, recent evidence indicates that neutral stimuli are not perceived as truly neutral by patients with schizophrenia or their first-degree relatives, thereby calling into question the interpretability of earlier findings. Second, few studies have explored brain connectivity in response to negative emotional faces in healthy relatives of patients, even though emotions are processed by a complex network of interconnected brain structures.

**Objective:** This study aims to investigate the neural mechanisms underlying emotion perception in patients with schizophrenia and their siblings, focusing on brain activation and functional connectivity during the perception of negatively valenced facial expressions. We employed a more ecologically valid task compared to previous studies, incorporating emotional faces within an emotionally charged context. By employing a well-matched control

condition and examining connectivity patterns within emotion-processing networks, we seek to address the limitations of prior research.

**Methods:** A total of 118 participants (37 patients with schizophrenia, 39 siblings of patients, and 42 healthy controls) took part in the study. Participants underwent functional magnetic resonance imaging (fMRI) scanning while performing an emotional task involving negatively valenced faces and control conditions. Behavioural performance was assessed using the Balanced Integration Score (BIS) to evaluate speed-accuracy tradeoffs. fMRI data were analysed for brain activation, using a complementary approach based on frequentist and Bayesian statistics, as well as for functional connectivity, using generalized psychophysiological interaction (gPPI) analysis with bilateral amygdala as seed regions.

**Results:** Behavioural analyses revealed significant group differences, with both patients and their siblings displaying lower BIS scores compared to healthy controls. Between-group fMRI analyses revealed that, compared to controls, siblings exhibited decreased brain activation to negative faces in a cluster encompassing the right superior temporal gyrus and right somatosensory cortex. Bayesian analyses suggest that patients may show similar impaired activation in the right somatosensory cortex. In most of the rest of the brain, including the amygdala, Bayesian analyses indicated an absence of group differences between both patients and siblings compared to healthy controls. Additionally, when compared to patients, siblings demonstrated lower activation in the bilateral postcentral gyrus and left superior occipital lobe. Functional connectivity analyses revealed that siblings had stronger task-related connectivity between the right amygdala and the right cuneus compared to healthy controls. When compared with patients, siblings also had stronger connectivity in the bilateral cuneus, left precentral gyrus, left cerebellum, and left superior temporal gyrus.

**Conclusion:** Our findings provide evidence that, while the amygdala appears to respond to negative faces similarly among controls, siblings, and patients, an endophenotypic pattern may be present in the right somatosensory cortex. Furthermore, these results suggest that activation-based analyses may not fully capture the neural abnormalities associated with emotion processing in relatives of patients with schizophrenia. We hypothesize that the increased connectivity between the right amygdala and the right cuneus may reflect a compensatory mechanism in siblings.

## **Introduction**

Schizophrenia is a complex psychiatric disorder that affects around 1% of the population worldwide. A core feature of the disorder is impairment in emotion processing, in particular, poorer emotion recognition performance. Indeed, numerous studies have shown that patients with schizophrenia have deficits in emotion perception, particularly during facial emotion processing (Chan et al., 2010; Kohler et al., 2010). These impairments are especially pronounced when processing negatively valenced facial expressions (Gao et al., 2021).

Interestingly, meta-analytical evidence suggests that first-degree relatives of individuals with schizophrenia also have difficulties in recognizing facial expressions, particularly those conveying negative emotions (Martin et al., 2015). These findings support the hypothesis that deficits in emotion processing could serve as a potential endophenotype of schizophrenia (Gur et al., 2007) -a measurable component along the pathway between the disease and the distal genotype, but less readily observed in healthy first-degree relatives of patients (Gottesman & Gould, 2003).

Neuroimaging measures are particularly valuable in this context, as they provide stable and reliable endophenotypes that are less susceptible to the variability of behavioral performance throughout the illness (Glahn et al., 2007; Gur et al., 2007; Hariri & Weinberger, 2003). However, whether brain correlates of emotion processing qualify as relevant endophenotypes of schizophrenia remains an open question. Two primary limitations may have hindered progress in this area.

First, in order to specifically study brain activity linked to emotional processing while controlling for visual confounds, functional magnetic resonance imaging (fMRI) studies have traditionally contrasted emotional stimuli to neutral ones. However, it recently became evident that neutral stimuli are not perceived as properly neutral in schizophrenia. This has been corroborated by recent findings reporting that brain activations in response to neutral stimuli differ between patients with schizophrenia and healthy controls (Dugré et al., 2019), with patients showing hyperactivity in the limbic system. Differences were also found between first-degree relatives of patients with schizophrenia and healthy controls (Fiorito et al., 2024), with relatives exhibiting hypoactivity in limbic areas.

As a result, it has been suggested that the hypoactivation in response to emotional stimuli in schizophrenia patients could be at least partially explained by hyperactivation to neutral stimuli (Anticevic et al., 2012; Dugré et al., 2019), thus calling into question our present comprehension of brain correlates of emotion processing in schizophrenia.

Second, it has been argued that coordinated activity across neural networks, rather than isolated activity within specific regions, is more reflective of complex behaviors like emotion processing (Meehan & Bressler, 2012). To investigate emotional face processing more effectively, advanced techniques capable of quantifying the direction and strength of connectivity between brain regions, such as psychophysiological interaction (PPI) analysis, are thus crucial (Gard et al., 2018). Notably, functional connectivity during emotion processing seems to be impaired in schizophrenia (Comte et al., 2017; Potvin et al., 2017). Furthermore, a handful of studies investigating brain connectivity during emotion processing have also observed differences in first-degree relatives (Cao et al., 2016; Diwadkar et al., 2012; Quarto et al., 2018).

Given these considerations, the current study aimed to investigate the neural mechanisms underlying emotion processing in patients with schizophrenia, their healthy first-degree relatives (i.e., siblings), and healthy controls, addressing the limitations identified in previous research. First, we examined brain activation during the processing of negatively valenced faces -that trigger the most severe behavioral deficits in both patients and siblings- using a well-matched control condition as a comparator. Second, we focused on functional connectivity, acknowledging that emotion processing is governed by a distributed network of interconnected brain structures. Using generalized psychophysiological interaction (gPPI) analysis with the bilateral amygdala as seed regions, we searched for disruptions in the coordinated activity within emotion processing networks, which could serve as a more sensitive and specific neural marker for schizophrenia.

## **Methods**

### **Participants**

122 participants took part in this study (40 patients with schizophrenia, 40 siblings of the included patients, and 42 healthy controls). Patients had a diagnosis of schizophrenia, established according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) and confirmed through a psychiatric interview. Patients were regularly monitored in an appropriate hospital setting and were not hospitalized. Additionally, the type and dosage of their medication treatment had remained stable for the past six months. Siblings (i.e., brothers and sisters) of patients with schizophrenia did not have psychiatric antecedents and did not take psychotropic treatments. Finally, healthy controls had no personal or family-related psychiatric antecedents and no psychotropic treatments.

This study was conducted following the principles of the Declaration of Helsinki. Approval was obtained from the local ethics committee (Comité de protection des personnes [CPP] Sud-Est III, Saint-Etienne). Each participant gave informed written consent before entering the study.

Three participants (2 patients and 1 sibling) were excluded from the analysis as they exited the MRI scanner before completing the scanning session, resulting in incomplete data acquisition. Furthermore, we excluded data from 1 patient due to excessive head motion during the anatomical scan. Thus, the final sample comprised 37 patients with schizophrenia, 39 siblings of the included patients, and 42 healthy controls.

### **Task**

We employed an emotional task that has been previously proven to be efficient for investigating the neural correlates of emotional processing: the variable attention and congruency task (VAAT, Comte et al., 2016). A detailed description of the task is provided elsewhere (Comte et al., 2016); briefly, the task comprises 4 sessions, and task stimuli are composed of two images: an emotional face in the central part and an emotional scene in the background. In each trial, participants have to focus on the part of the image highlighted in green (either the face or the scene) and report if it depicts a positive or negative emotion, using a two-button response box. The stimulus remains displayed on the screen for 3 seconds,



during which the participant answers. Moreover, in a control condition, participants must determine whether an arrow appearing either in the central part of the image or in the background is pointing toward the left or right direction.

Unlike traditional tasks used to study emotional processing in schizophrenia, which typically involve the isolated presentation of faces displaying different emotions, this task offers a more ecologically valid approach by integrating both facial expressions and contextual emotional cues. This method more closely mirrors real-life situations, where we not only interpret emotions from facial expressions but also from the emotional context in which interactions occur.

In the context of the present study, we employed this task to address limitations observed in prior research and to enhance our understanding of emotional processing in schizophrenia. Specifically, we focused on conditions that more closely replicate the previous literature, investigating behavioral and brain responses when participants focused on negatively valenced faces in the absence of an emotional incongruency (i.e., where both the face and background scene expressed negative emotional valence), referred to as "negative faces".

### **Behavioural analyses**

Statistical analyses were performed with Matlab (version R2020b) and R (version 4.3.1).

While traditional behavioral analyses often treat accuracy and reaction time as independent variables, this approach can obscure the interplay between speed and performance, particularly in tasks where a tradeoff exists. Thus, to assess the speed-accuracy tradeoff in our study, we used the Balanced Integration Score (BIS, Liesefeld & Janczyk, 2019). This metric is designed to integrate both accuracy and reaction time with equal weight into a single measure. It corresponds to the difference between standardized accuracy and standardized reaction time (RT) of correct answers:

$$BIS_{i,j} = Z_{Accuracy_{i,j}} - Z_{RT_{i,j}} \text{ with } Z_{x_{i,j}} = \frac{x_{i,j} - \bar{x}}{SD_x}$$

Where  $i$  is the participant and  $j$  is the condition. The standardized scores ( $z$ ) are calculated across all subjects and conditions. Since higher accuracy and lower reaction times indicate better performance in a task, a higher BIS indicates a better overall task performance.

Using *ezANOVA* function in R, we run an analysis of variance (ANOVA) with one within-group factor (BIS score for negative faces) and one between-subject factor (group, with 3 levels: patients with schizophrenia, siblings, healthy controls). For significant results, we perform post-hoc pairwise t-tests using Tukey's HSD (honestly significant difference) procedure.

### **fMRI Data Acquisition**

Functional MRI data were acquired on a 3T Siemens MAGNETOM Prisma scanner at the IRMAS Centre (Saint-Etienne Hospital Centre, France) using a T2\*-weighted echo-planar imaging (EPI) sequence. The protocol parameters were as follows: repetition time (TR) = 2.32 s, echo time (TE) = 30 ms, flip angle = 90°, field of view (FOV) = 220. Each volume consisted of 45 slices with a slice thickness of 3 mm, resulting in a voxel size of  $3 \times 3 \times 3 \text{ mm}^3$ .

Structural images were acquired using a T1-weighted magnetization-prepared rapid gradient-echo (MPRAGE) sequence, providing high-resolution anatomical images. The parameters for the structural scan were as follows: TR = 2.8 s, TE = 2.27 ms, inversion time (TI) = 1100 ms, flip angle = 8°, FOV = 230, 256 slices, and voxel size of  $1 \times 1 \times 1 \text{ mm}^3$ .

### **fMRI Preprocessing**

The fMRI data were preprocessed using the fMRIPrep pipeline (version 23.0.1; Esteban et al., 2020, 2019). This automatic workflow performs minimal preprocessing on both anatomical and functional data.

For the anatomical preprocessing, the T1-weighted images were corrected for intensity non-uniformity, skull-stripped, and segmented into cerebrospinal fluid, white matter, and grey matter. Spatial normalization to MNI standard space (MNI152NLin2009cAsym) was performed using nonlinear registration.

For the functional preprocessing, the 4 blood-oxygen-level-dependent (BOLD) runs underwent slice-timing correction and were realigned for head motion correction. Field distortion

correction was applied using B0 field maps, which were estimated from the phase-drift map of two consecutive Gradient Echo acquisitions and aligned to the Echo-planar imaging (EPI) reference image. The corrected images were then co-registered to the T1-weighted reference, followed by spatial normalization to MNI space (using voxel dimension of 2 x 2 x 2 mm<sup>3</sup>). Finally, functional images preprocessed with fmriprep were smoothed with a 6 mm full-width at half-maximum (*FWHM*) Gaussian kernel.

## **fMRI statistical analysis**

### *Functional activity*

The fMRI data were analysed using statistical parametric mapping (SPM12; Wellcome Center for Neuroimaging, London, UK; <https://www.fil.ion.ucl.ac.uk/spm>) implemented in MATLAB (version R2020b) on a Unix computer. Part of the analyses were performed with bidsfm (v3.1.0dev; <https://github.com/cpp-lin-lab/bidsfm>; Van Audenhaege et al., 2024).

At the subject level, we performed a mass univariate analysis with a linear regression (General Linear Model, GLM) at each voxel of the brain, using generalized least squares. Image intensity scaling was done run-wide before statistical modelling such that the mean image would have a mean intracerebral intensity of 100.

We modelled the fMRI data using an event-related design, with regressors entered into the run-specific design matrix. The task manipulated three factors, each with two levels, following a 2 x 2 x 2 design: emotional valence (negative or positive), attention (faces or scenes), and congruency (congruent or incongruent scene-face valence). This resulted in eight conditions, each represented by a separate regressor of interest. All regressors were convolved with a canonical hemodynamic response function (HRF). Given the short duration of response time, each trial was modelled as an event, thus considering the duration of neural activity as an impulse (i.e., zero duration).

For the denoising strategy, we followed guidelines for task-based fMRI (Mascali et al., 2021), and included several nuisance covariates in our GLM: 24 movement regressors parameters (including 6-realignment parameters, their temporal derivatives, and squared terms) to control for movement, and anatomical component correction strategy (aCompCor)

introduced by Behzadi et al. (2007), to control for physiological noise. To prevent data overfitting, we retained a fixed number of principal components, 5 for each tissue type (white matter and cerebrospinal fluid). Data were also high-pass filtered (128 s) to remove low-frequency signals, and a FAST model was applied to adjust for serial correlations in the data.

For each participant, we generated a first-level contrast modelling brain responses to negative faces in the context of a congruent negative background scene compared to the control condition [Negative Faces > Control Condition].

The first-level contrasts were then entered into a second-level one-sample t-test to examine within-group activations. We employed ANOVA to investigate between-group differences in activation, using the group as a factor. Two sample t-tests were used for two-by-two group comparisons (patients versus healthy controls; siblings versus healthy controls; patients versus siblings). Results were thresholded using a cluster-defining threshold of  $p < 0.001$  and a cluster significance threshold of  $p < 0.05$  familywise error (FWE) corrected.

To complement classical second-level frequentist analyses, we employed a Bayesian approach to quantify evidence in favor of the null hypothesis. Specifically, we employed the BayesFactorFMRI toolbox (Han, 2020, 2021), a tool developed with R and Python code to perform Bayesian voxel-wise analysis of T-maps at the second level. This toolbox was customized (by HH) to conduct two-sample t-tests for two-by-two group comparisons, producing a map of Bayes factors (BF) for each voxel. The BF is the ratio of the likelihood of the data under the null hypothesis ( $H_0$ , hypothesizing the absence of meaningful group differences) and the likelihood of the same data under the alternative hypothesis ( $H_1$ , hypothesizing a meaningful group difference).  $BF_{01}$  quantifies the evidence supporting  $H_0$  relative to  $H_1$ , while  $BF_{10}$  ( $= 1/BF_{01}$ ) quantifies the evidence supporting  $H_1$  relative to  $H_0$ . Conventionally a  $BF_{01}$  (or  $BF_{10}$ ) that exceeds the threshold of 3 represents moderate evidence in favor of  $H_0$  (or  $H_1$ ), while a BF between 10 and 30 represents strong evidence (Jeffreys, 1998). Results are thus reported at a threshold of  $BF > 3$ . It should be noted that BayesFactorFMRI adjusts the prior probability distribution to address the problem of multiple comparisons. Nonetheless, the main results concerning the presence of group differences were derived from classical frequentist whole-brain analyses with stringent multiple comparison corrections.

### *Functional connectivity*

Generalized psychophysiological interaction (gPPI, McLaren et al., 2012) was employed to investigate whether the pattern of functional connectivity differed between groups. Given the key role of the amygdala in emotion processing, the left and right amygdala were used as seeds in two separate gPPI analyses. To define the seed mask, we created a 5 mm sphere centred on the amygdala, using the peak coordinates of the one sample activations across all groups. Within the seed region, the first eigenvariate of the BOLD time series was extracted and deconvolved with the canonical HRF to generate the physiological regressor. Then, PPI regressors were created as the product of the seed time course and task regressors. We run a first-level GLM with the physiological regressor of the seed region, the psychological regressors of the task, and the PPI regressors, as well as all the nuisance variables (24 movement regressor, 5 CompCor for the white matter and 5 CompCor for cerebrospinal fluid). We followed the same procedure as for activation analyses, and we created a first-level contrast [Negative Faces > Control Condition]. Finally, as for activation analyses, we used a one-sample t-test for within-group analyses and ANOVA with group as a factor, followed by two sample t-tests for two-by-two between-group comparisons. Results were thresholded using a cluster-defining threshold of  $p < 0.001$  and a cluster significance threshold of  $p < 0.05$  familywise error (FWE) corrected.

## Results

### Participants demographic characteristics

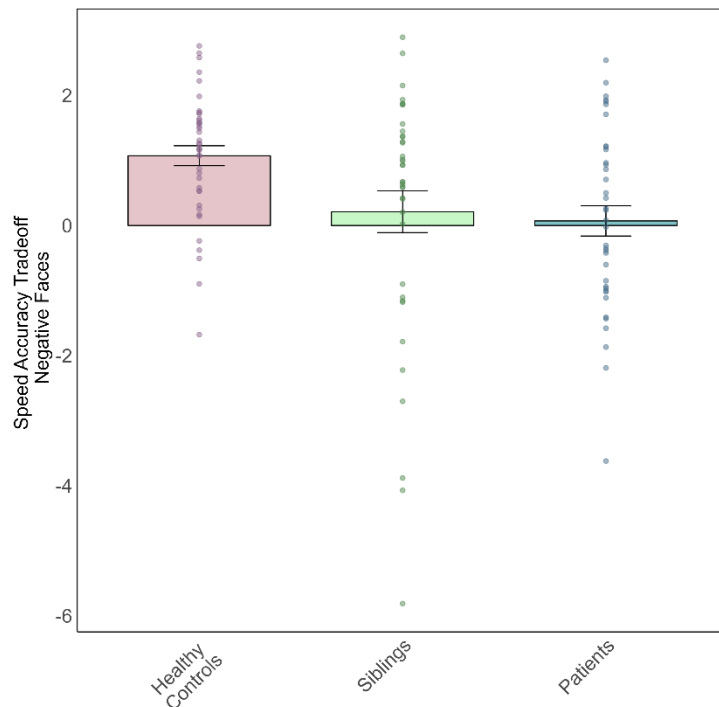
The groups did not significantly differ in age. However, there was a significant difference in years of education between patients and healthy controls (mean difference = -1.6 years, 95% CI [-2.9, -0.3],  $p = 0.01$ ). Additionally, the sex distribution of siblings differed significantly from that of patients (mean difference = -0.48, 95% CI [-0.73, -0.23],  $p < 0.001$ ) and healthy controls (mean difference = -0.26, 95% CI [-0.50, -0.02],  $p = 0.03$ ). See Table 1 for participants demographic characteristics.

|  | Healthy Controls | Siblings   | Patients with schizophrenia |
|--|------------------|------------|-----------------------------|
| Number   | 42               | 39         | 37                          |
| Age (years); SD  | 36.5 ± 8.9       | 34.7 ± 9.6 | 35.1 ± 8.0                  |
| Sex (M/F)  | 25/17            | 13/26      | 30/7                        |
| Education (years); SD                                    | 13.1 ± 1.5       | 18.9 ± 2.9 | 11.5 ± 2.8                  |
| Positive and Negative Syndrome Scale (PANSS) - Total; SD |                  |            | 39.1 ± 16.8                 |
| <i>Positive</i>  | /                | /          | 6.5 ± 5.8                   |
| <i>Negative</i>  |                  |            | 14.9 ± 6.8                  |
| <i>General</i>   |                  |            | 18.7 ± 8.9                  |
| Chlorpromazine equivalent (mg/day; SD)                   | /                | /          | 541.9 ± 450.1               |

**Table 1.** Participant's demographic characteristics.

### Behavioural analyses

The ANOVA revealed a significant main effect of the group ( $F = 5.192$ ,  $p = 0.007$ ). Post-hoc comparisons using the Tukey HSD test indicated that siblings had a BIS score significantly lower than healthy controls (mean difference = -0.86, 95% CI [-1.67, -0.06],  $p = 0.033$ ). Patients also scored significantly lower than healthy controls (mean difference = -1.00, 95% CI [-1.81, -0.20],  $p = 0.010$ ). Finally, the difference between patients and their siblings was not statistically significant (mean difference = -0.14, 95% CI [-0.96, 0.68],  $p = 0.912$ ). See Figure 1 for a barplot depicting the behavioural results.



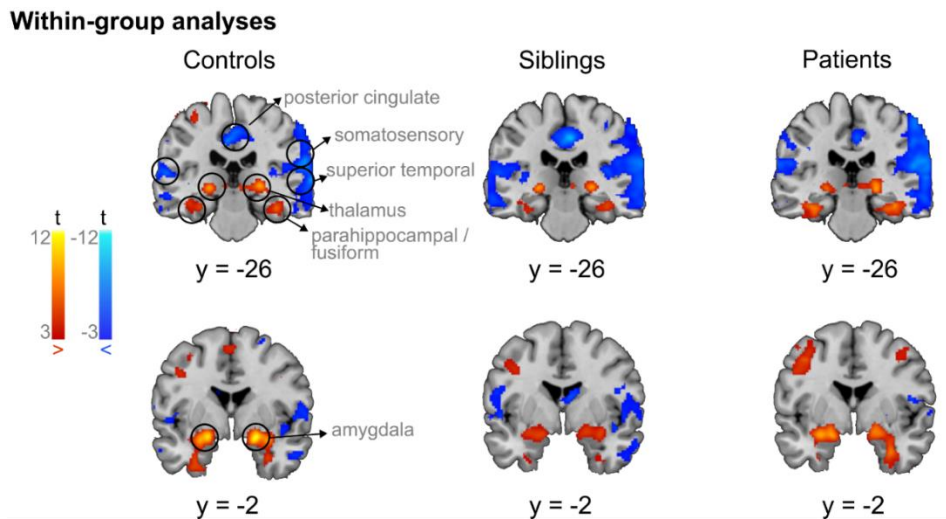
**Figure 1.** Barplot illustrating the Speed Accuracy Tradeoff scores (measured by the Balanced Integration Score, BIS) for the Negative Faces condition across the three groups: healthy controls, siblings, and patients with schizophrenia. We observed an endophenotypic pattern, with siblings exhibiting BIS scores that were intermediate between those of patients and healthy controls. The height of each bar represents the group's mean BIS score, with error bars representing  $\pm 1$  standard error of the mean. Individual data points are overlaid to show participant-level variability within each group.

### **fMRI analyses - Brain activation**

#### Within-group analyses

Within each group, the one-sample t-test for Negative Faces > Control Condition identified significant activations across multiple brain regions commonly associated with emotional face processing, such as bilateral amygdala, thalamus, and fusiform face areas. Several deactivations were also observed, particularly in regions of the Default Mode Network (DMN), comprising the bilateral ventromedial prefrontal cortex (vmPFC), precuneus, and posterior cingulate cortex. Decreased activations were also observed in bilateral cuneus, somatosensory cortex, superior temporal gyrus, middle inferior temporal gyrus, and cerebellum during negative faces compared with the control condition.

The pattern of brain (de-)activations was consistent across patients with schizophrenia, their siblings, and healthy controls (see Figure 2 for detailed brain activation patterns in each group).



**Figure 2.** Results of within-group brain activation analyses in healthy controls, siblings, and patients with schizophrenia. Brain regions showing significantly increased activations toward negative faces compared to the control condition are depicted in red, and deactivations are depicted in blue. As expected, the task activated regions involved in emotion processing, while deactivations were observed in regions of the DMN. Results are thresholded using a cluster-forming threshold of  $p < 0.001$  and a cluster significance threshold of  $pFWE < 0.05$ .

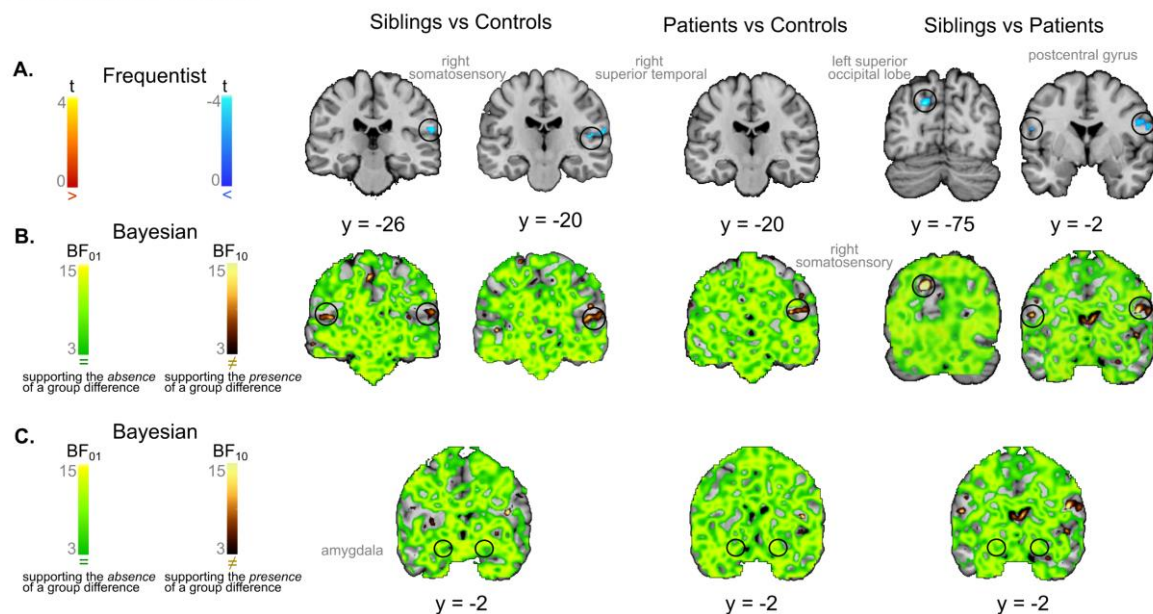
The ANOVA identified a significant group effect in the left occipital lobe. Subsequent two-sample t-tests showed that siblings exhibit reduced activation in a cluster encompassing the right superior temporal gyrus and the right somatosensory cortex. Additionally, comparisons between patients and siblings revealed decreased brain activity in siblings in the bilateral postcentral gyrus and the left superior occipital lobe. Following correction for multiple comparisons, no significant differences were observed between patients and controls (see Figure 3A).

For each group comparison, Bayesian analyses supported the absence of activation differences, with Bayes Factors ( $BF_{01}$ ) exceeding 3, across the majority of brain voxels, including the bilateral amygdala (see Figure 3C). Several clusters exhibited at least moderate evidence of differences in brain activation between groups ( $BF_{10} > 3$ ). These clusters were



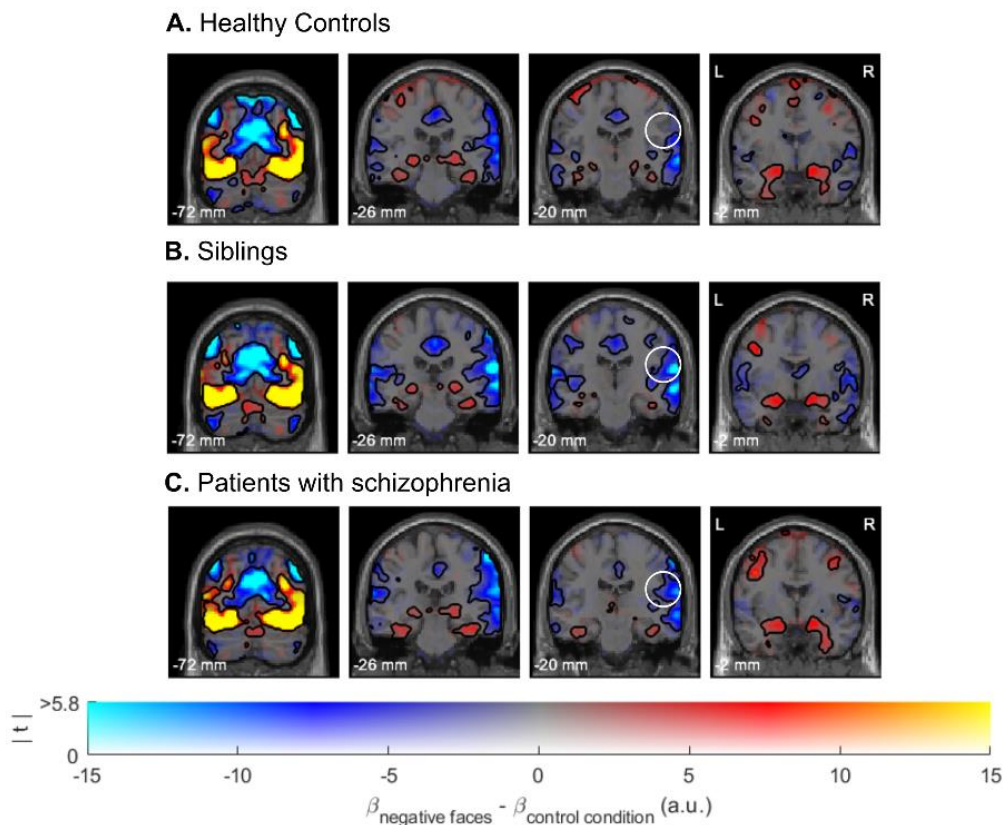
mostly in accordance with frequentist analyses. However, since Bayesian analyses use a less stringent procedure for multiple comparison corrections, which does not take into account cluster size, small clusters that are not in accordance with frequentist results are assumed to reflect false positives. Although these findings may be less robust, it is noteworthy that, in addition to confirming significant differences between siblings and healthy controls in a right-lateralized cluster comprising of superior temporal gyrus and somatosensory cortex, Bayesian analyses also revealed evidence of group differences in a contralateral cluster in the left hemisphere. Additionally, Bayesian comparisons between patients and healthy controls revealed a cluster in the right somatosensory cortex where the Bayes Factors favoured the alternative hypothesis (see Figure 3B). Note that this is a two-tailed test, which does not indicate the direction of these differences, however, the directionality can be inferred by examining the unthresholded beta contrasts from the frequentist analyses, as depicted in dual-coded Figure 4. As illustrated in this figure, Bayesian analyses provide evidence indicating a reduction in activation within this cluster in patients compared to healthy controls.

#### Between-group analyses



**Figure 3.** Results of between-group two-sample analyses. For frequentist analyses (A.), hyperactivations are depicted in red, and hypoactivations in blue. Results are thresholded with a cluster-forming threshold of  $p < 0.001$  and a cluster significance threshold of  $p_{FWE} < 0.05$ . For Bayesian analyses (B.-C.), voxels with at least moderate (or higher) evidence supporting the absence of differences between groups are depicted in green ( $BF_{01} > 3$ ). Voxels

with at least moderate (or higher) evidence supporting the presence of a group difference are depicted in gold ( $BF_{10} > 3$ ). Results are thresholded at  $BF > 3$ . Bayesian analyses not only replicate the frequentist findings but also extend them by revealing a potential endophenotypic pattern in the right somatosensory cortex (B.). Additionally, these analyses provide evidence for the absence of group differences in the amygdala (C.). All functional maps are overlaid on the Colin 27 anatomical template.



**Figure 4.** Results of within-group brain activation analyses using dual-coded images (Allen et al., 2012; Zandbelt, 2017). In these images, colour represents the contrast estimate -the difference between the beta values for negative faces and the beta values for the control condition, expressed in arbitrary units. Red regions indicate activations, while blue regions indicate deactivations. Transparency represents t-values, which are computed by dividing the beta values by their estimated standard errors, thus accounting for the variability of the data. Black line contours denote significant (de-)activations at a threshold of  $p_{FWE} < 0.05$ . The white circle surrounding the cluster in the right superior temporal gyrus and somatosensory

*cortex highlights significant activation differences between siblings and healthy controls. All functional maps are overlaid on the SPM12 anatomical template.*

### ***fMRI analyses - Functional connectivity***

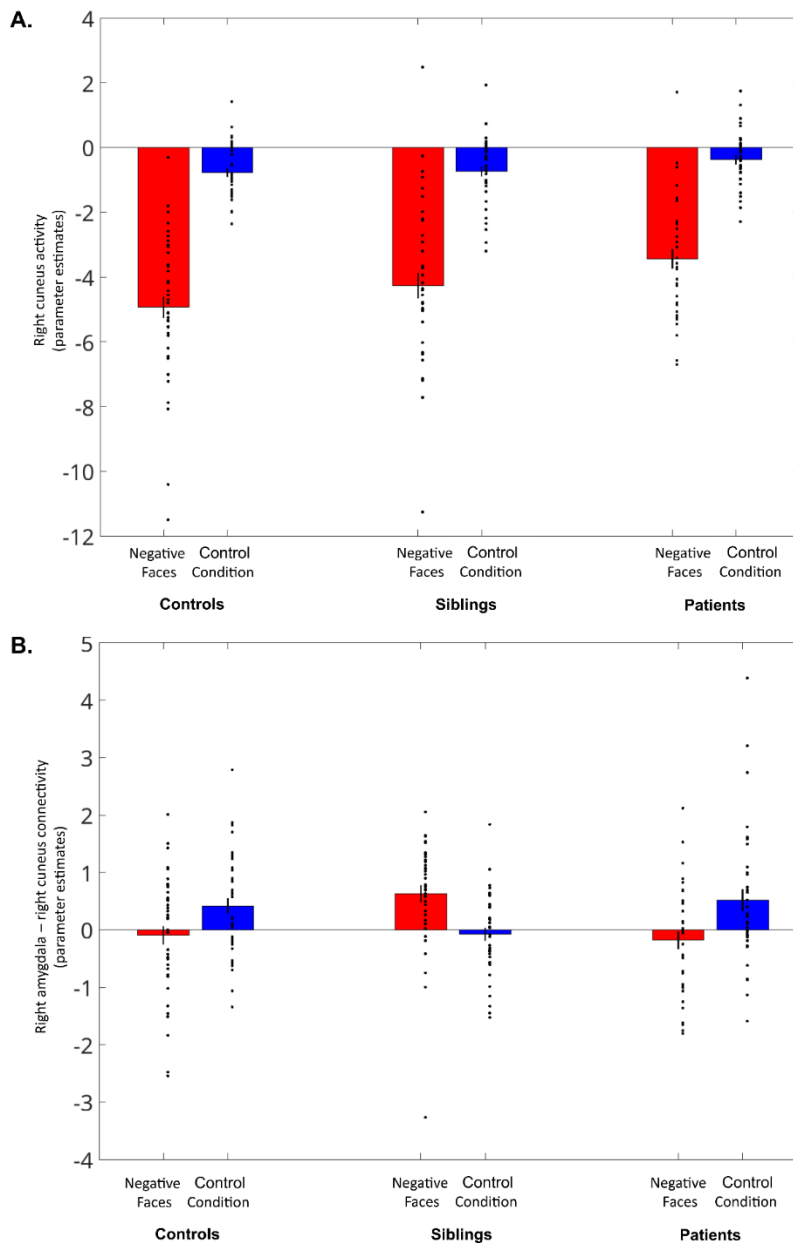
#### *Within-group analyses*

gPPI analyses within each group revealed that when siblings attended to negative faces, the right amygdala's time course was more strongly correlated with the right cuneus than when they performed the control condition. In patients, there was a task-dependent decreased connectivity between the right amygdala and left postcentral gyrus. No significant differences in coupling were observed while using the left amygdala as the seed region. Furthermore, negative faces versus control conditions were not associated with a reliable change in functional connectivity in healthy controls.

#### *Between-group analyses*

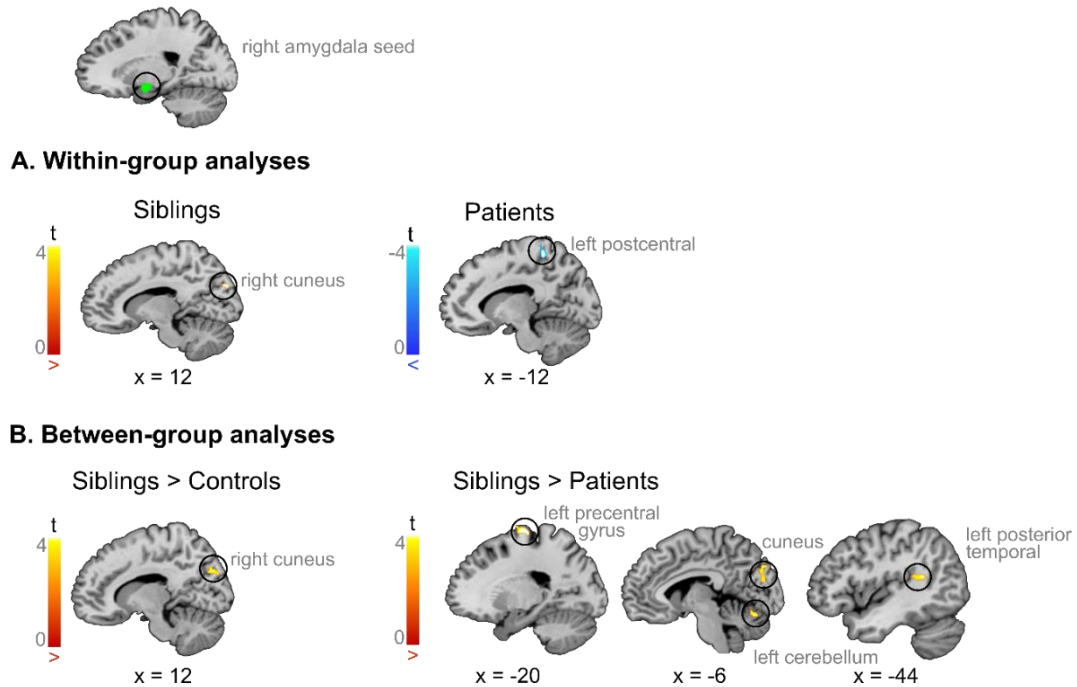
In response to negative faces versus control condition, the ANOVA showed an effect of the group in the connectivity between the right amygdala and the right cuneus. Two-by-two comparisons revealed that siblings exhibited stronger task-related functional connectivity between the right amygdala and the right cuneus compared to healthy controls. We used the voxels in the right cuneus showing this connectivity difference to create a mask, and subsequently extracted and plotted both activation and connectivity with the right amygdala across the three groups using *rfxplot* (Gläscher, 2009) (see Figure 5). While activation in the right cuneus followed a qualitative endophenotypic pattern, with intermediate values in siblings relative to healthy controls and patients, the connectivity between the right cuneus and the right amygdala exhibited an opposite pattern in siblings compared to both healthy controls and patients.

Moreover, when siblings were compared with patients with schizophrenia, they showed increased connectivity between the right amygdala seed and bilateral cuneus and the left posterior temporal gyrus, left precentral gyrus, and left cerebellum. No significant differences between groups in functional connectivity were observed when comparing patients with schizophrenia and healthy controls. See Figure 6 for between-group results.



**Figure 5.** Barplot illustrating the modulation of the right cuneus activity (A.) and of the task-related connectivity between the right cuneus and the right amygdala (B.) as a function of the condition (Negative Faces, Control Condition) and the group (controls, siblings, patients). The parameter estimates of the beta values were extracted from a mask of the right cuneus, defined as those voxels showing increased task-related connectivity with the right amygdala in siblings as compared with healthy controls. While an endophenotypic pattern was observed in the activity of the right cuneus, siblings showed an opposite pattern of connectivity between the right cuneus and the right amygdala relative to both controls and

patients. Individual data points are displayed, with error bars representing the standard error of the mean.



**Figure 6.** Results of connectivity analyses using the right amygdala as the seed of the PPI. For within-group analyses (A.), and between-group analyses (B.). Increased connectivity with the right amygdala is depicted in red, and decreased connectivity in blue. Siblings exhibited increased connectivity between the right amygdala and right cuneus, which was significantly greater than that observed in both controls and patients. Results are thresholded with a cluster-forming threshold of  $p < 0.001$  and a cluster significance threshold of  $p_{FWE} < 0.05$ . All functional maps are overlaid on the Colin 27 anatomical template.

## Discussion

The current study aimed to investigate the neural mechanisms underlying the perception of negative emotional faces in patients with schizophrenia, their healthy first-degree relatives (siblings), and healthy controls. Our findings provide evidence that siblings of patients with schizophrenia exhibit both behavioral and neural impairments compared to healthy controls. This supports the growing body of literature suggesting that such impairments may already be present in individuals at genetic risk for schizophrenia, indicating a potential genetic component underlying these deficits.

Using an ecological emotional task, we observed that both patients with schizophrenia and their siblings exhibited poorer performance in recognizing negative facial expressions, as reflected by lower BIS. Importantly, by integrating both reaction times and accuracy, the BIS provides a more accurate reflection of overall task efficiency. This finding is consistent with previous research showing that patients with schizophrenia have impaired emotion recognition, particularly for negatively valenced expressions (Chan et al., 2010; Gao et al., 2021; Kohler et al., 2003). Although both patients and siblings performed worse than healthy controls, no significant difference was observed between these two groups. However, as qualitatively illustrated in the bar plot (see Figure 1), siblings exhibited slightly milder deficits. These results align with earlier meta-analytic findings of first-degree relatives of individuals with schizophrenia exhibiting difficulties in recognizing facial expressions, particularly negative emotions (Martin et al., 2015).

At the neural level, our whole-brain activation analysis demonstrated that patients, siblings, and healthy controls all engaged regions commonly associated with emotion processing, including the bilateral amygdala, thalamus, and fusiform face areas. This finding is consistent with our expectations, as the emotional task was specifically designed to robustly engage brain circuits involved in emotion processing, as demonstrated in prior fMRI studies (Comte et al., 2016). We also observed greater engagement of the DMN during the control condition, which required less cognitive effort, compared with the negative faces. This aligns with previous research indicating increased involvement of the DMN across varying levels of cognitive effort (Weber et al., 2022).

When comparing brain activations between siblings and healthy controls, we observed reduced activation in a cluster comprising the right superior temporal gyrus and the right somatosensory cortex in siblings. Although this finding did not survive a stringent correction for multiple comparisons in frequentist analyses, Bayesian analyses revealed bilateral hypoactivation in this region among siblings compared to healthy controls, reinforcing the robustness of this result. These findings suggest that siblings may exhibit subtle but detectable alterations in neural responses to negative emotional faces, even in the absence of a clinical diagnosis.

The superior temporal gyrus has been strongly implicated in the pathogenesis of schizophrenia. A recent meta-analysis of 246 MRI studies revealed that patients with schizophrenia exhibit volume reductions in this region (Kuo & Pogue-Geile, 2019). Additionally, reduced cortical connectivity with the superior temporal gyrus has also been observed in both patients and their relatives (Oertel-Knöchel et al., 2013). Finally, evidence for the involvement of this region in the transition to schizophrenia comes from studies reporting gray matter reduction in this region in both first-episode psychosis and ultrahigh-risk individuals who subsequently developed psychosis at 12-month follow-up, as compared to those who did not (Takahashi et al., 2009).

Previous studies have also frequently reported structural and functional deficits in the postcentral gyrus, which encompasses the somatosensory cortex, in the schizophrenia continuum. Notably, decreased gray matter volume has been observed in chronic patients, particularly in those with adolescent-onset schizophrenia (Zhang et al., 2017), as well as in individuals with first-episode psychosis (Job et al., 2002), with further reductions at one-year follow-up (Ferro et al., 2015). Moreover, there is substantial evidence of hypoconnectivity within the somatosensory network (Dong, Wang, Chang, et al., 2018). Alterations of its connection to the thalamus have also been observed (Kaufmann et al., 2015; Li et al., 2017). Interestingly, this region has been associated with emotion recognition performances in schizophrenia. Indeed, a 10-week emotion recognition training in patients with schizophrenia demonstrated increased activation in the right postcentral gyrus, which could predict behavioral improvements (Hooker et al., 2012).

Reduced activation in the right superior temporal gyrus and sensorimotor cortex observed in siblings of patients may have significant implications for emotion perception. This finding aligns with the right hemisphere hypothesis, which suggests that emotional processing and related behaviors are predominantly lateralized to the right hemisphere (Demaree et al., 2005). Additionally, these regions are involved in the theory of mind (Bodden et al., 2013; Caillaud et al., 2020; Mier et al., 2010) and the embodiment of emotions (Barrett, 2017; Kropf et al., 2019). Emotion recognition is closely related to these functions, as accurately identifying others' emotions often requires the ability to adopt their perspective and involves the simulation of their affective states via somatosensory representation (Adolphs et al., 2000; Mitchell & Phillips, 2015). While remaining cautious with reverse inference and post-hoc interpretation, we suggest that the reduced involvement of the right superior temporal gyrus and somatosensory cluster in siblings of schizophrenia patients may indicate diminished engagement in the higher-level cognitive processes essential for social cognition.

Furthermore, Bayesian analyses provide evidence in favor of the absence of differences between siblings and controls across most of the voxels of the brain, and particularly in the amygdala (see Figure 3C). This is in line with our previous meta-analysis showing no reliable differences between individuals at enhanced risk of schizophrenia and healthy controls, with strong evidence in the bilateral amygdala (Fiorito et al., 2022).

We did not observe significant brain activation differences between patients and healthy controls, with evidence in favor of the absence of group differences across several voxels of the brain comprising the bilateral amygdala (see Figure 3C). This contrasts with previous meta-analytical findings reporting decreased activations, notably in limbic regions, in schizophrenia (Dong, Wang, Jia, et al., 2018b; Li et al., 2010; Taylor et al., 2012). However, our findings are consistent with the hypothesis that the hypoactivations observed in patients may have been, at least partially, overestimated due to the use of neutral stimuli as a comparator in fMRI studies (Anticevic et al., 2012; Dugré et al., 2019; Fiorito et al., 2024).

It is important to note that Bayesian analyses revealed at least moderate evidence of differences between patients with schizophrenia and healthy controls within a cluster in the right somatosensory cortex. This finding may suggest a shared pathway affecting both patients and their siblings, indicating impairments in higher-level emotional processing, rather than



implicating amygdala dysfunction as traditionally hypothesized when using neutral stimuli as comparators. We thus suggest that the observed reductions could indicate a potential endophenotypic marker. However, this result should be interpreted with caution due to its lack of replication in classical frequentist analyses. The absence of significant differences might be attributed to substantial variability among patients (as suggested by dual-color Figure 4). Schizophrenia is an exceptionally heterogeneous disorder with diverse clinical manifestations, biological predispositions, and environmental influences. Stratifying patients into subgroups with distinct pathophysiological and clinical profiles may enhance our understanding of the underlying mechanisms and provide deeper insights into the complexity of the disorder. Such an approach may also help in identifying and validating more robust endophenotypes.

We also observed decreased activation of the bilateral postcentral gyrus and the left superior occipital lobe in siblings as compared with patients. Since patients were under medication treatment, antipsychotics may compensate for brain abnormalities. Indeed, previous research suggests that antipsychotic drugs lead to network topologies that are closer to those of healthy subjects (Towlson et al., 2019). Alternatively, the observed differences might reflect compensatory neural adaptations reflecting protective mechanisms at play in the siblings.

Functional connectivity analyses using gPPI revealed notable differences in siblings compared with healthy controls, showing increased task-related connectivity between the right amygdala and right cuneus. This result reinforces the notion that traditional activation-based analyses may not fully capture the neural abnormalities associated with emotion processing in schizophrenia risk.

Interestingly, it has been proposed that while the left amygdala could be more involved in language-related processing of affective information, the right amygdala treats image-related affective information (Markowitsch, 1998).

The cuneus is a region of the visual cortex that receives visual input from the contralateral superior retina. Research indicates that emotion and stress may influence its function. Indeed, studies using electroencephalography have reported that the C1 component, which primarily originates in the cuneus, is enhanced in response to fearful faces but not neutral or happy faces, thus showing that negative emotions may modulate the early stages of visual processing

via their impact on the cuneus (Raftopoulos, 2023). Additionally, previous research supports a dual-route model for processing negative facial expressions, as proposed by LeDoux (1996). This model suggests that only the processing of negative emotions, unlike positive ones, activates both cortical (right cuneus to right amygdala) and subcortical (right thalamus to right amygdala) pathways (Liu et al., 2015). Following acute stress, reduced connectivity between the amygdala and the cuneus has been observed (Ford et al., 2022; Quaedflieg et al., 2015), while recovery from stress has been associated with increased functional connectivity between the amygdala and the cuneus (Quaedflieg et al., 2015). Additionally, elevated peripheral inflammatory markers have been linked to reduced amygdala-cuneus connectivity during negative face recognition (Swartz et al., 2022). Beyond its role in primary visual processing, the cuneus appears to contribute to working memory (Bomyea et al., 2017; He et al., 2021; Owens et al., 2018), and to the regulation of emotions associated with negative autobiographical memories (Kross et al., 2009).

The cuneus has been previously implicated in schizophrenia pathogenesis, by findings showing decreased gray matter volume (Mané et al., 2009; Yu et al., 2018), impaired dynamic functional connectivity at rest (Nyatega et al., 2021), and decreased activations during retrieval of episodic memory -the part of the memory more closely linked to the emotional component (Ragland et al., 2009). Recent meta-analytical results also showed decreased activations in the cuneus during theory of mind tasks in patients as compared to healthy controls (Jáni & Kašpárek, 2018; Weng et al., 2022). Reduced activity in the cuneus has also been reported in previous studies investigating emotional faces as compared to scrambled ones in healthy first-degree relatives of patients with schizophrenia (Spilka et al., 2015).

Few studies have investigated brain connectivity in first-degree relatives of patients with schizophrenia, reporting notable findings. One study using dynamic causal modeling (DCM) reported reduced driving inputs to the V1 area in the offspring of patients with schizophrenia during an emotional n-back paradigm involving visual faces (Diwadkar et al., 2012). This finding could not be replicated in a subsequent study, since the authors did not include visual areas in their model (Quarto et al., 2018). However, similar results were reported in another study that utilized correlation-based network analyses to investigate functional connectivity (Cao et al., 2016). In this study, they observed decreased coupling in first-degree relatives

among several generations (but mostly including offspring) in several nodes of the limbic system, including the amygdala and visual cortex areas such as the cuneus, during emotional face processing (Cao et al., 2016).

When extracting both activation and connectivity estimates from the right cuneus, we observed an endophenotypic pattern for activation, with intermediate activation estimates in siblings, and an opposite pattern of connectivity with the right amygdala in siblings compared with healthy controls and patients. Based on this observation, and in light of previous literature indicating reduced connectivity between the amygdala and cuneus during negative face processing in the offspring of patients with schizophrenia (Cao et al., 2016; Diwadkar et al., 2012), we speculate that the increased connectivity between the right amygdala and the right cuneus may represent a compensatory mechanism in low-level areas of face emotion processing in siblings of patients with schizophrenia. Notably, previous studies primarily investigated brain connectivity in children of patients with schizophrenia, while our study included siblings who are older and thus considered less at risk due to their age. Interestingly, enhanced recruitment of the cuneus has recently been proposed as a functional compensation mechanism, particularly in healthy aging, which may facilitate the processing of multiple features of a stimulus (Knights et al., 2024). Furthermore, it has been suggested that genetic resilience in schizophrenia may emerge through the strengthening of visual pathways (Hettwer et al., 2022).

We did not observe brain connectivity differences between patients with schizophrenia and healthy controls. When comparing siblings with patients with schizophrenia, we observed reduced connectivity in patients between the right amygdala and bilateral cuneus, left precentral gyrus, left superior temporal gyrus, and left cerebellum. It has been shown that individuals with cannabis use disorder have decreased functional connectivity between the amygdala and the cuneus (Aloi et al., 2021). Since 26% of patients with schizophrenia present a comorbid cannabis use disorder (Hunt et al., 2018), and 42% of patients had a lifetime use of cannabis (Green et al., 2005), cannabis consumption may have had an impact on the observed results.

This study has several limitations. First, the sample size is relatively small. Nevertheless, a key strength of this study is the inclusion of both patients and siblings from the same families, in

contrast to previous research that often examines these groups separately. This approach helps mitigate the influence of environmental factors, as it controls for shared familial and environmental variables that could otherwise confound the results. Large-scale studies should replicate these findings. The inclusion of a large number of participants should also allow the investigation of brain-behavior correlations. Indeed, it has been suggested that such associations between brain functioning and complex cognitive phenotypes require samples with thousands of individuals to be reliable (Marek et al., 2022). Second, the groups included in this study were not comparable in terms of sex and education level, which may have introduced a bias in our results. Third, all patients were undergoing medication treatment. Although we included only those who had been stable (with no changes in treatment or dosage for at least six months), it is acknowledged that antipsychotics can affect brain structure and function. Future research should investigate emotional brain correlates in individuals with first-episode psychosis who have not yet received medication treatment. Finally, in this study, we were unable to clearly differentiate between risk factors, protective factors, or compensatory mechanisms. Future longitudinal studies that follow relatives who transition to schizophrenia and those who do not will be crucial.

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## CHAPITRE IV - Peut-on cartographier des anomalies de la microglie dans la schizophrénie ?

*[Article #4]*

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Les endophénotypes, en tant que marqueurs intermédiaires entre le niveau génétique et les manifestations cliniques des troubles psychiatriques, ont une composante génétique fondamentale. Ils permettent de mieux comprendre les mécanismes sous-jacents à la schizophrénie, en identifiant des processus biologiques spécifiques, influencés par des facteurs génétiques qui sont perturbés chez les patients et leurs apparentés.

Comme résumé dans l'introduction, nos connaissances actuelles sur les facteurs génétiques de la schizophrénie ont surtout mis en évidence le rôle du complexe majeur d'histocompatibilité, codant pour des gènes en lien avec la **fonction immunitaire** (Ripke et al., 2014 ; Trubetskoy et al., 2022). Cette association a montré être en partie liée au gène C4, qui code pour le composant 4 du système du complément, un groupe de protéines qui participe à la réponse immunitaire (Sekar et al., 2016).

Mais le principal acteur de cette fonction immunitaire dans le système nerveux central est la **microglie**, une population de cellules gliales représentant environ 10 % des cellules cérébrales, soit une proportion similaire à celle des neurones. Il est désormais bien établi que le rôle de la microglie va bien au-delà de la simple réponse inflammatoire. En coordination avec le système du complément, la microglie joue un rôle crucial dans le processus d'**élagage synaptique**, qui a lieu durant le développement postnatal. Ce processus semble altéré dans la schizophrénie, qui serait caractérisée par un élagage excessif. En effet, un nombre réduit de synapses a été observé dans le cerveau post-mortem de patients atteints de schizophrénie comparé à des sujets contrôles (Berdens van Berlekom et al., 2020). Il a été proposé que cette réduction des synapses se reflète morphologiquement par une diminution de l'épaisseur corticale (Selemon & Goldman-Rakic, 1999), qui est influencée génétiquement (Winkler et al., 2010). Ainsi, cette altération structurelle pourrait non seulement affecter la morphologie cérébrale, mais également entraîner des modifications dans le fonctionnement des réseaux neuronaux, influençant potentiellement les processus cognitifs et émotionnels sous-tendus par ces régions.

La microglie apparaît comme un point de rencontre clé dans la schizophrénie, étant impliquée à la fois dans l'*hypothèse inflammatoire*, par son rôle dans la réponse immunitaire, et dans le processus d'*élagage synaptique*, un mécanisme postnatal susceptible de favoriser le développement de la maladie (Feinberg, 1982), conformément aux *théories neurodéveloppementales* (Johnson & Hyman, 2022). De plus, la microglie pourrait également servir de médiateur dans l'interaction entre vulnérabilité et stress, conformément au *modèle stress-vulnérabilité* prédominant dans la schizophrénie (Howes and McCutcheon, 2017). Par exemple, une étude chez la souris a montré que l'exposition prénatale à des défis immunitaires, comme une infection, augmente la vulnérabilité aux changements cérébraux en réponse au stress durant la puberté, via une réponse exagérée de la microglie, un phénomène de « *priming* » se traduisant par une réponse plus intense à des stimuli répétés (Giovanoli et al., 2013).

Enfin, un nouveau champ de recherche, appelé « immunologie affective », est en train d'émerger, visant à explorer les liens cellulaires et moléculaires entre les émotions et le système immunitaire (D'Acquisto, 2017). Ainsi, l'inflammation pourrait être un facteur déterminant dans le fonctionnement des régions cérébrales responsables des émotions. Des recherches ont en effet montré qu'une activation immunitaire maternelle chez la souris entraîne la libération de cytokines pro-inflammatoires dans l'embryon, et que ce profil inflammatoire persiste dans l'amygdale jusqu'au début de l'âge adulte (O'Loughlin et al., 2017). De plus, suite à ce type d'inflammation des altérations morphologiques des cellules gliales, notamment la microglie, ont été observées dans l'amygdale postnatale (O'Loughlin et al., 2017). Il a également été démontré que chez des sujets contrôles, une inflammation aiguë réduit la capacité à interpréter les émotions des autres (Moieni et al., 2015), tout en perturbant l'activité des régions émotionnelles (Inagaki et al., 2012).

Traditionnellement, l'activation microgliale a été classée en deux états : la microglie M1, induisant l'inflammation et la neurotoxicité, et la microglie M2, jouant un rôle anti-inflammatoire et neuroprotecteur. Cependant, cette classification binaire ne reflète pas entièrement la complexité de l'activité microgliale. Il est maintenant proposé que l'analyse des composants moléculaires de la microglie puisse offrir une vue plus sophistiquée de son

activité. Ainsi, plusieurs études ont montré une altération au niveau de l'**expression génétique** de la microglie, comme rapporté par exemple dans la méta-analyse de Snijders et collaborateurs (2021). Cependant, aucune étude n'a cartographié dans la schizophrénie les altérations d'expression génétique de la microglie dans différentes régions cérébrales. De plus, des études précédentes suggèrent que ces altérations pourraient également être retrouvées dans les tissus périphériques, où les macrophages expriment de nombreux gènes de la microglie (Bergon et al., 2015).

Dans une quatrième étude, nous avons voulu apporter une contribution à notre compréhension de l'implication de la microglie dans la pathophysiologie de la schizophrénie (*Article #4, Fiorito et al., Transl Psychiatry, 2023*). Nous avons utilisé 9 ensembles de données d'expression génétique indépendantes, accessibles en Open Access dans la **base de données Gene Expression Omnibus**, afin d'examiner l'expression des gènes de la microglie. Pour limiter le nombre de comparaisons multiples, nous avons sélectionné un nombre restreint de gènes appartenant à une signature microgliale humaine, définie à travers une approche déterminée a priori. Nous avons inclus 8 régions cérébrales et 3 tissus périphériques, couvrant un total de **267 individus atteints de schizophrénie et 237 sujets contrôles**. La collecte des données, la sélection des gènes candidats de la microglie, les hypothèses et les analyses statistiques ont été préenregistrées. Nos résultats ont montré une **diminution dans l'expression** génétique des gènes de la microglie dans quatre régions cérébrales différentes (**cervelet, striatum associatif, hippocampe et cortex pariétal**). De plus, nous avons identifié une expression différentielle des gènes de la microglie, également exprimés par les macrophages périphériques, dans le sang total d'individus atteints de schizophrénie. Nos résultats renforcent le rôle de la microglie dans la physiopathologie de la schizophrénie, offrant un aperçu de l'hétérogénéité régionale du cerveau. Ils soutiennent également l'utilisation d'échantillons de **sang comme biomarqueurs neurobiologiques potentiels**.

Cette base de données a l'inconvénient de ne fournir qu'un nombre limité de jeux de données concernant des tissus ou des populations spécifiques. Par conséquent, les recherches futures devront analyser l'expression génétique de la microglie dans d'autres tissus, notamment dans les régions cérébrales associées au traitement émotionnel. En outre, explorer ces

modifications chez des apparentés permettrait de déterminer la présence d'éventuelles altérations et d'évaluer si celles-ci présentent un potentiel héréditaire.

**Article #4**

Anna M. Fiorito, Eric Fakra, Guillaume Sescousse, El Chérif Ibrahim and Romain Rey.

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

*Translational Psychiatry*, 13, 386 (2023). <https://doi.org/10.1038/s41398-023-02677-y>

The study was preregistered on AsPredicted.org (#67610, <https://aspredicted.org/285rn.pdf>)

# Résumé graphique Article #4 - présenté au congrès de NeuroFrance, Lyon (France), mai 2023



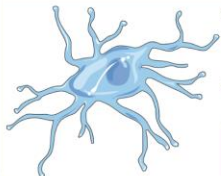
## MOLECULAR MAPPING OF MICROGLIA-SPECIFIC GENES IN SCHIZOPHRENIA

Anna Fiorito<sup>a,b</sup>, Eric Fakra<sup>a,b</sup>, Guillaume Sescousse<sup>a,c</sup>, El Chérif Ibrahim<sup>d</sup>, Romain Rey<sup>a,c,e</sup>

<sup>a</sup> Lyon Neuroscience Research Center, INSERM U1028, CNRS UMR5292, PSYR2 Team, University of Lyon, Lyon, France <sup>b</sup> Department of Psychiatry, University Hospital of Saint-Etienne, Saint-Etienne, France <sup>c</sup> Centre Hospitalier Le Vinatier, Bron, France <sup>d</sup> Aix-Marseille Université, CNRS, INT, Institut de Neurosciences de la Timone, Marseille, France <sup>e</sup> Fondation FondaMental, Créteil, France

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### BACKGROUND

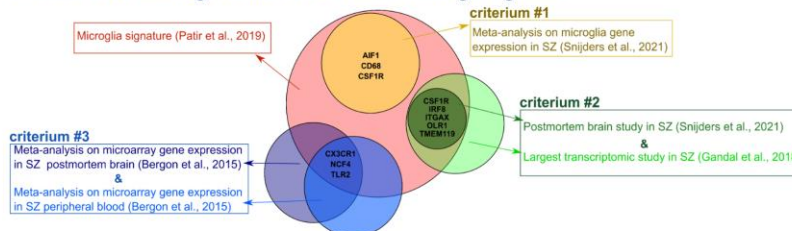


- Microglia, resident macrophage cells, account for about 10-15% of cells within the brain
- Microglia play a key role in several processes involved in schizophrenia (SZ) pathogenesis (e.g., immunity, inflammation, synaptic pruning, neurogenesis)
- Microglia gene expression is altered in SZ suggesting its role in SZ etiopathology

However **regional specificity** and **peripheral expression** of microglia/macrophages genes in SZ remains unknown

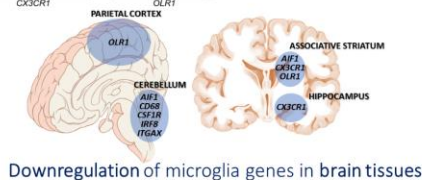
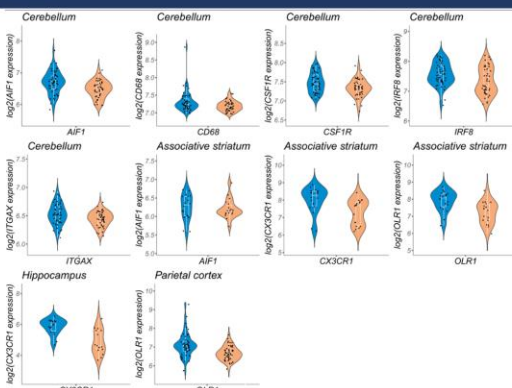
### METHODS

- Pre-registered on AsPredicted.org (#67610)
- Selection of candidate genes from a core human microglia signature

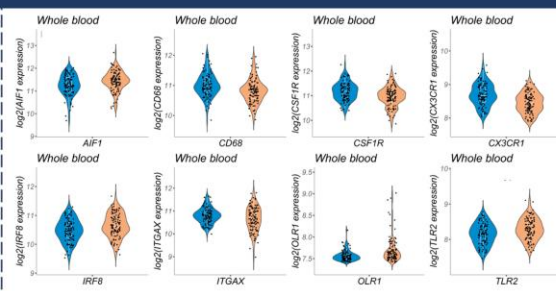


- Selection of datasets through Gene Expression Omnibus (GEO) database: 9 datasets from 8 brain regions and 3 peripheral tissues (764 samples from 267 SZ and 237 HC)
- Each dataset analyzed independently
- Fold Change (FC) =  $\bar{x}_{HC} - \bar{x}_{SZ}$  Two-tailed t-test/Welch/Mann-Whitney (adjusted with False Discovery Rate)

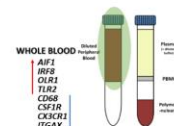
### RESULTS



Downregulation of microglia genes in brain tissues



status  
■ Healthy controls  
■ Individuals with schizophrenia



Altered expression of microglia/macrophages genes in peripheral tissues

### CONCLUSIONS

- Brain underexpression of microglia genes may represent a candidate transcriptional signature for SZ
- Dual brain-blood alterations support SZ as a whole-body disorder and the use of blood samples as a potential source of biological peripheral biomarkers



## ARTICLE OPEN



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

Anna M. Fiorito<sup>1,2</sup>, Eric Fakra<sup>1,3</sup>, Guillaume Sescousse<sup>1,2</sup>, El Chérif Ibrahim<sup>4</sup> and Romain Rey<sup>1,2,5</sup>✉

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Besides playing a central role in neuroinflammation, microglia regulate synaptic development and is involved in plasticity. Converging lines of evidence suggest that these different processes play a critical role in schizophrenia. Furthermore, previous studies reported altered transcription of microglia genes in schizophrenia, while microglia itself seems to be involved in the etiopathology of the disease. However, the regional specificity of these brain transcriptional abnormalities remains unclear. Moreover, it is unknown whether brain and peripheral expression of microglia genes are related. Thus, we investigated the expression of a pre-registered list of 10 genes from a core signature of human microglia both at brain and peripheral levels. We included 9 independent Gene Expression Omnibus datasets (764 samples obtained from 266 individuals with schizophrenia and 237 healthy controls) from 8 different brain regions and 3 peripheral tissues. We report evidence of a widespread transcriptional alteration of microglia genes both in brain tissues (we observed a decreased expression in the cerebellum, associative striatum, hippocampus, and parietal cortex of individuals with schizophrenia compared with healthy controls) and whole blood (characterized by a mixed altered expression pattern). Our results suggest that brain underexpression of microglia genes may represent a candidate transcriptional signature for schizophrenia. Moreover, the dual brain-whole blood transcriptional alterations of microglia/macrophage genes identified support the model of schizophrenia as a whole-body disorder and lend weight to the use of blood samples as a potential source of biological peripheral biomarkers.

*Translational Psychiatry* (2023)13:386; <https://doi.org/10.1038/s41398-023-02677-y>

## INTRODUCTION

Schizophrenia (SZ) is a complex polygenic disorder [1] whose onset typically arises during adolescence. Over the past decade, results from genome-wide association studies have allowed researchers to identify hundreds of variants associated with the SZ risk, shedding light on SZ pathogenesis. Indeed, the interaction of multiple genetic factors with each other and with environmental risk factors is thought to result in pathological neurodevelopmental processes underlying SZ. To date, the strongest genetic association involves the Major Histocompatibility Complex locus [2, 3]. In humans, this locus is essentially related to immune function.

Accordingly, the role of immunity and inflammation in SZ is now largely recognized [4], while microglia, the resident immune cells of the central nervous system, has raised increasing interest [5]. Remarkably, microglia are not only involved in immunity and inflammation but are also required by the developing brain for critical neurodevelopmental processes such as synaptic pruning [6, 7] or neurogenesis regulation [8] which have been involved in the pathophysiology of SZ [9–12].

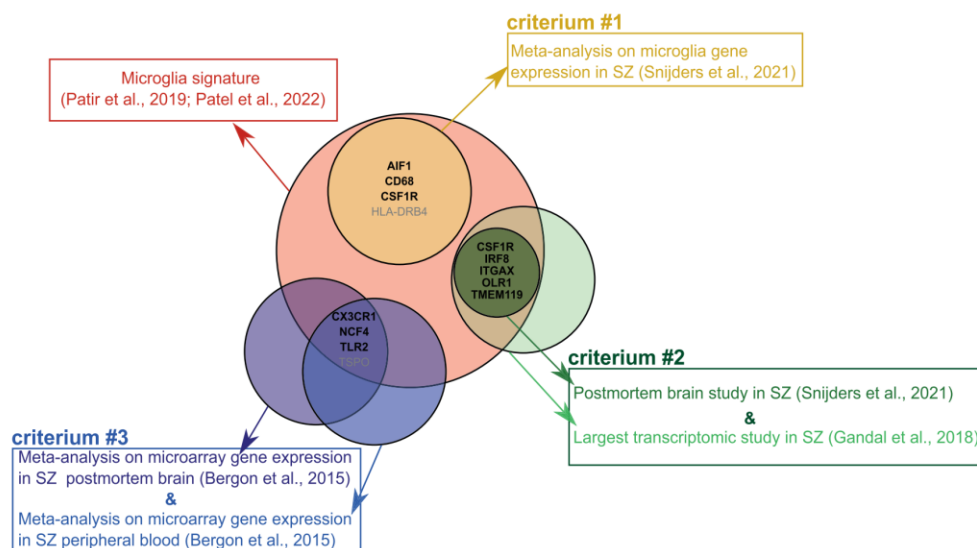
In this light, some studies have looked for more direct evidence of microglia dysfunction in individuals with SZ, using techniques such as translocator protein (TSPO) positron emission tomography (PET) (microglia activation) and immunohistochemistry in

postmortem samples (microglia morphology and density). However, various meta-analyses summarizing these studies reported inconsistent results [13–16]. Poor cellular type specificity or insufficient sensitivity may explain the TSPO-PET heterogeneous results [17], while microglia density and morphology are too simplistic parameters which only offer a partial picture of microglia functioning.

Microglia function has also been explored by gene expression studies which are more specific and more likely to accurately reflect the complex nature of microglial functioning. A meta-analysis of such studies in human postmortem tissues obtained from various brain regions found an overall decreased microglia gene expression in individuals with SZ compared with healthy controls (HCs) [15]. Although supporting the dysregulation of microglia in SZ, Snijders et al.'s results have three major limits. Firstly, the meta-analytic results were pooled from various brain regions precluding finer conclusions regarding a potential region heterogeneity of microglia alterations in SZ. Secondly, the original studies included in the meta-analytic work didn't explore the same candidate genes across included studies, thus preventing meta-analytic results at the gene level. Finally, presence of a publication bias was confirmed by Egger's test, suggesting the meta-analysis was biased towards positive results.

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Received: 26 June 2023 Revised: 20 November 2023 Accepted: 22 November 2023  
Published online: 13 December 2023



**Fig. 1 Selection of candidate genes.** Venn diagram depicting the procedure of selection of candidate genes. Only genes that were part of a core transcriptional signature of human microglia [21, 22] were included. Based on previous work, we identified microglia genes that seems to be altered in schizophrenia (SZ) according to three criteria. Firstly, we selected all the genes differentially expressed in individuals with SZ compared with healthy controls (HCs) in at least one of the studies included in the meta-analysis of Snijders et al. [15] (criterion #1). Secondly, we selected genes differentially expressed both in a postmortem study exploring candidate genes [15] and in the largest transcriptomic study to this day in SZ [100], as reported in Snijders et al. [15] (criterion #2). Thirdly, we selected genes that were consistently differentially expressed in individuals with SZ compared with HCs in a meta-analysis including results from postmortem brain and peripheral tissues samples [19] (criterion #3). Included genes are noted in black bold font.

In light of these limits, more studies are needed to replicate and extend current knowledge regarding dysregulation of microglia gene expression in individuals with SZ. Such studies should systematically explore the same set of candidate microglia-specific genes in various brain regions of individuals with SZ compared with HCs, allowing the identification of abnormal transcription at the region level. Furthermore, while postmortem studies allow the investigation of SZ pathogenesis through direct access to brain tissues, there is a dire need for readily accessible SZ biomarkers. In this regard, peripheral tissues are a promising method to probe the transcriptome in a minimally invasive way and allow for the identification of biological peripheral biomarkers of SZ disorder [18]. Noteworthy, in SZ, blood-based microarray meta- [19] and mega- [20] analyses revealed differentially expressed genes involved in immunologic functions, including microglia-related genes.

Using Gene Expression Omnibus (GEO) datasets, in this study we aimed to explore the expression of microglia genes at the central and peripheral levels in individuals with SZ compared with HCs. Notably, the present study takes into account the various limitations of current literature regarding microglia gene expression studies in SZ. Especially, we systematically explored in 8 different brain regions and 3 peripheral tissues a set of 10 genes selected through a comprehensive approach and belonging to a core transcriptional signature of human microglia [21, 22]. There was no overlap between the data used in the present study and that from Snijders et al.'s meta-analysis [15], allowing us to produce new results replicating, refining and expanding current knowledge regarding SZ-associated microglia alterations.

## MATERIAL AND METHODS

Data collection, selection of candidate microglia genes, hypotheses, and statistical analyses were pre-registered on AsPredicted.org (#67610, <https://>

[aspredicted.org/285rn.pdf](https://aspredicted.org/285rn.pdf)), on March 6th, 2021. It should be noted that datasets included in this study were slightly different from those pre-registered (see Supplementary Methods for further details on this deviation from the pre-registration).

## Inclusion of genes from a core human signature of microglia

To limit the number of multiple comparisons (associated with an increase of Type I errors) and the subsequent lack of power associated with false discovery rate corrections, we limited the number of candidate genes, which were selected using a comprehensive approach. See Fig. 1 for details on selection of candidate genes.

## Search and inclusion criteria of dataset

Datasets were searched through GEO database, a public repository which archives and freely distributes genomic data from postmortem brain or peripheral tissues samples obtained from HCs and patients suffering from various disorders [23]. With the aim to identify altered expression of microglia genes both at the central and peripheral level in individuals with SZ, we explored the GEO database for datasets providing gene expression results from individuals with SZ and HCs.

We included datasets compliant with data extraction through shinyGEO [24], an application implemented using R [<https://www.r-project.org/>], shiny [<http://shiny.rstudio.com/>] and GEOquery package [25]. Using GEO database, we therefore searched for studies on SZ, using homo sapiens as the primary organism, and filtering by gene series and microarray technology.

We included datasets obtained from original studies using samples from SZ and HC individuals, and providing microarray-derived gene expression results acquired from postmortem brain samples (not restricted to the neuronal cell population) or peripheral tissues samples.

## Demographic characteristics and quality data

For each GEO dataset, the quality data of the samples (i.e., RNA integrity number (RIN), brain pH, postmortem interval) and the demographic characteristics (i.e., age and sex) of the subjects who provided brain or peripheral tissues are summarized in Tables 1–2.

**Table 1.** Demographic and quality characteristics of the postmortem brain samples.

| Brain region                         | Subjects (n) | Age (mean ± SD) |               | Sex (M/F)            |              | Postmortem interval (mean ± SD) |                      |               | brain pH (mean ± SD) |                      |             | RIN (mean ± SD) |                   | p-value <sup>a</sup> |             |         |
|--------------------------------------|--------------|-----------------|---------------|----------------------|--------------|---------------------------------|----------------------|---------------|----------------------|----------------------|-------------|-----------------|-------------------|----------------------|-------------|---------|
|                                      |              | HC              | SZ            | p-value <sup>a</sup> | HC           | SZ                              | p-value <sup>a</sup> | HC            | SZ                   | p-value <sup>a</sup> | HC          | SZ              | HC                |                      | SZ          |         |
| Hippocampus<br>GSE53987              | 18 HC, 15 SZ | 48.16 ± 10.95   | 45.73 ± 8.79  | 0.493                | 9/9          | 9/6                             | 0.729                | 19.39 ± 5.2   | 19.4 ± 7.2           | 0.994                | 6.61 ± 0.21 | 6.43 ± 0.31     | 0.065             | 7.37 ± 0.64          | 6.54 ± 0.52 | <0.001* |
| Associative striatum<br>GSE53987     | 18 HC, 18 SZ | 48.44 ± 10.82   | 45 ± 8.75     | 0.301                | 10/8         | 10/8                            | 1                    | 19.75 ± 5.14  | 19.9 ± 7.07          | 0.945                | 6.59 ± 0.23 | 6.47 ± 0.37     | 0.233             | 8.21 ± 0.69          | 7.87 ± 0.80 | 0.182   |
| Anterior PFC<br>GSE17612             | 23 HC, 28 SZ | 69.04 ± 21.55   | 73.32 ± 15.2  | 0.776                | 11/11 + 1 NA | 19/9                            | 0.251                | 9.9 ± 4.39    | 8.71 ± 6.98          | 0.058                | 6.5 ± 0.29  | 6.15 ± 0.21     | 0.001*            | -                    | -           | -       |
| Cerebellum<br>GSE53974               | 50 HC, 44 SZ | 45.8 ± 9.33     | 43.18 ± 9.53  | 0.208                | 31/19        | 32/12                           | 0.283                | 27.58 ± 11.13 | 33.27 ± 15.45        | 0.033*               | 6.47 ± 0.32 | 6.43 ± 0.25     | 0.297             | -                    | -           | -       |
| Parietal cortex<br>GSE53977          | 50 HC, 51 SZ | 45.5 ± 8.99     | 42.65 ± 9.87  | 0.132                | 35/15        | 37/14                           | 0.828                | 27.3 ± 11.82  | 31.39 ± 15.53        | 0.124                | 6.51 ± 0.31 | 6.37 ± 0.29     | 0.018*            | -                    | -           | -       |
| Superior temporal cortex<br>GSE21935 | 19 HC, 23 SZ | 67.68 ± 22.24   | 72.17 ± 16.94 | 0.742                | 10/9         | 13/10                           | 1                    | 9.12 ± 4.33   | 7.13 ± 5.75          | 0.023*               | 6.49 ± 0.32 | 6.16 ± 0.17     | 0.001*            | -                    | -           | -       |
| DLPFC-BA46<br>GSE53987               | 19 HC, 15 SZ | 48.05 ± 10.65   | 46 ± 8.64     | 0.549                | 10/9         | 7/8                             | 1                    | 19.53 ± 5.09  | 18.91 ± 6.69         | 0.763                | 6.59 ± 0.22 | 6.53 ± 0.39     | 0.542             | 7.85 ± 0.62          | 7.65 ± 0.68 | 0.376   |
| Frontal cortex<br>GSE2191            | 30 HC, 29 SZ | 43.5 ± 8.57     | 42.34 ± 8.95  | NS <sup>b</sup>      | 23/7         | 23/6                            | 1                    | 29.97 ± 12.71 | 31.40 ± 16.93        | NS <sup>b</sup>      | 6.61 ± 0.28 | 6.45 ± 0.25     | 0.01 <sup>b</sup> | -                    | -           | -       |

HC healthy controls, SZ individuals with schizophrenia, SD standard deviation, M/F male/female, RIN RNA Integrity Number, PFC prefrontal cortex, DLPFC dorsolateral prefrontal cortex, NA not available, NS not significant.

<sup>a</sup>*p* < 0.05.

<sup>b</sup>Unpaired *t*-test and Fisher exact tests were conducted to assess group differences for continuous and discrete variables, respectively.

<sup>c</sup>As reported in ref. [101].

## Ethical statement

All the data used in this project were acquired in previous studies, all of which conformed to ethical standards [26–33].

## Statistical analyses

JASP software (Version 0.11.1) was used to perform statistical analyses on gene expression data downloaded with shinyGEO. Gene expression values are already Log2-transformed to stabilize the variance and descriptive statistics of Log2 values in brain and peripheral tissues are provided in Supplementary Table 1. The fold change expression (FC) was computed as the difference between the average expression of HCs and the average expression of individuals with SZ.

Normal distribution and homogeneity of variances were tested using Shapiro-Wilk and Levene's tests, respectively. For differential expression, exact *p*-values were calculated using unpaired two-tailed *t* tests. In case of violation of the equal variance assumption, exact *p*-values were calculated using Welch tests. When a deviation from normality was detected, exact *p*-values were calculated using Mann-Whitney *U* tests. The resulting *p*-values were adjusted with the Benjamini and Hochberg's approach to control the false discovery rate. Gene expression comparisons were considered to be statistically significant for adjusted *p*-values < 0.05.

For genes that were significantly differentially expressed in individuals with SZ as compared with HCs, ANCOVA was used to evaluate the impact of potential confounding variables on candidate genes' expression. Each candidate gene expression was separately entered as a dependent variable, the group (individuals with SZ or HCs) was used as a fixed factor, while demographic and quality characteristics, when available, were used as covariates (i.e., age, sex, RIN, brain pH, and postmortem interval).

## Bayesian analyses

Additional Bayesian analyses were performed. Particularly, Bayesian two-sample *t* tests were conducted in JASP for genes that were significantly differentially expressed in individuals with SZ as compared with HCs in frequentist analyses. These analyses allowed to quantify the evidence in favor of the alternative hypothesis ( $H_1$ , hypothesizing the presence of a group difference) as well as the null hypothesis ( $H_0$ , hypothesizing the absence of a group difference) through inspection of the Bayes Factors (BFs). See Supplementary Methods for more details on Bayesian analyses.

## RESULTS

### Microglia genes

The present study investigated a pre-registered list of genes that are part of a core human microglia signatures [21, 22]. This list comprises the following 10 genes: *AIF1*, *CD68*, *CSF1R*, *CX3CR1*, *IRF8*, *ITGAX*, *NCF4*, *OLR1*, *TLR2*, *TMEM119*. Besides *TMEM119* [34], all the included genes are also expressed in peripheral macrophages. See Fig. 1 and Supplementary Methods for details on selection of candidate genes.

### Included datasets

The systematic search in the GEO database, which identified records published until July 6th, 2022, yielded a total of 88 datasets (see Supplementary Fig. 1 for the flow chart). After applying inclusion criteria, the number of datasets was filtered to a total of 12 eligible datasets.

Eventually, 9 GEO datasets were included in the present study (see Supplementary Fig. 1 and Supplementary Methods for details on the selection procedure and exclusions). The included GEO datasets consist of 764 samples obtained from 266 individuals with SZ and 237 HCs. They provided data from 8 different brain regions relevant to SZ (cerebellum, associative striatum, hippocampus, anterior prefrontal cortex (BA10), dorso-lateral prefrontal cortex (DLPFC, BA46), superior temporal cortex (BA22), and broad sections of the frontal cortex and parietal cortex) and 3 peripheral tissues (whole blood, peripheral blood mononuclear cells (PBMCs), and skin fibroblasts) (see Tables 1–2 for sample sizes, demographic and quality characteristics of included datasets). The original studies from which the included datasets were obtained are presented in Supplementary Table 2.

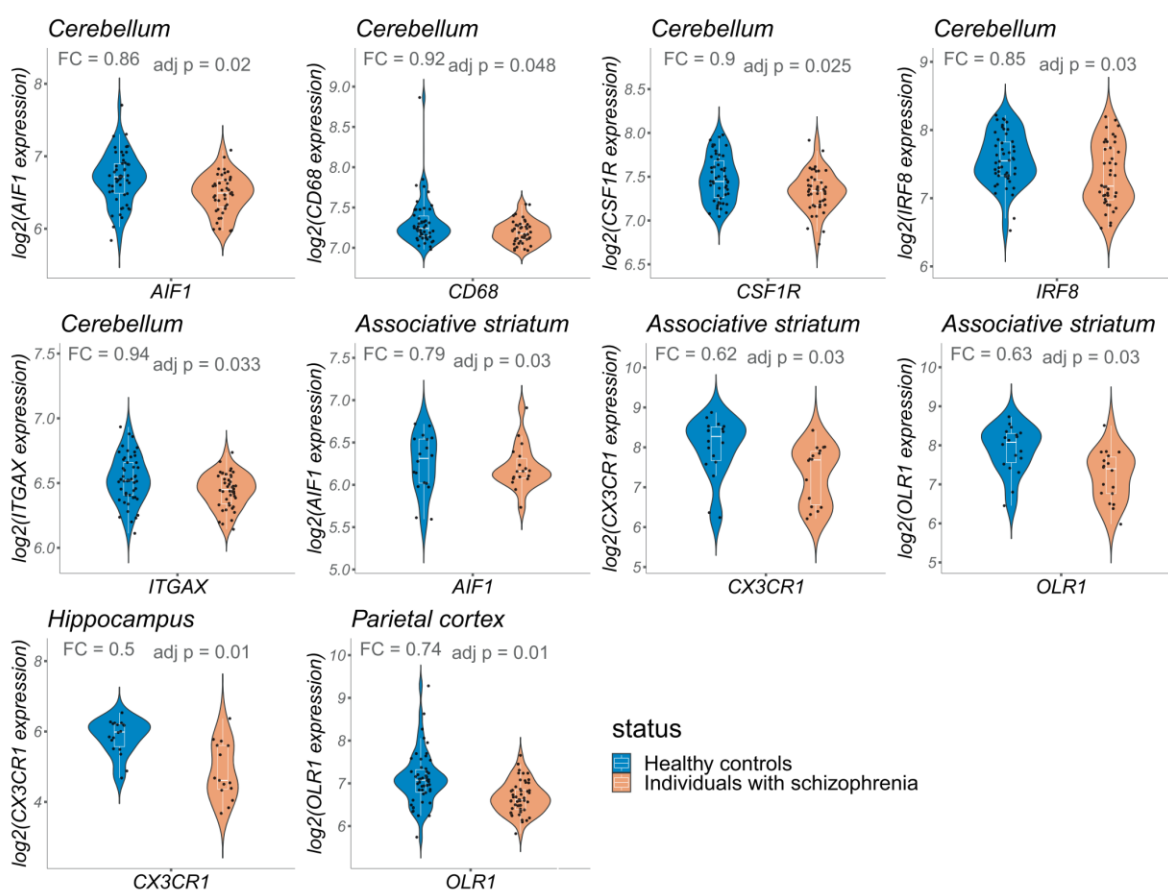
**Table 2.** Demographic and quality characteristics of the peripheral tissues.

| Brain region                    | Subjects (n)  | Age (mean $\pm$ SD) |                   |                      | Sex (M/F) |       |                      |
|---------------------------------|---------------|---------------------|-------------------|----------------------|-----------|-------|----------------------|
|                                 |               | HC                  | SZ                | p-value <sup>1</sup> | HC        | SZ    | p-value <sup>1</sup> |
| Blood (whole blood)<br>GSE38484 | 96 HC, 106 SZ | 39.31 $\pm$ 14.19   | 39.58 $\pm$ 10.74 | 0.538                | 42/54     | 76/30 | 0.001*               |
| Blood (PBMCs)<br>GSE27383       | 29 HC, 43 SZ  | 23.90 $\pm$ 4.08    | 23.02 $\pm$ 4.03  | 0.378                | 29/0      | 43/0  | 1                    |
| Skin fibroblasts<br>GSE62333    | 20 HC, 20 SZ  | 48.4 $\pm$ 12.2     | 44.6 $\pm$ 12.67  | 0.340                | 9/11      | 10/10 | 1                    |

HC healthy controls, SZ individuals with schizophrenia, SD standard deviation, M/F male/female, PBMC peripheral blood mononuclear cell.

\* $p < 0.05$ .

<sup>1</sup>Unpaired *t* test and Fisher exact tests were conducted to assess group differences for continuous and discrete variables, respectively.



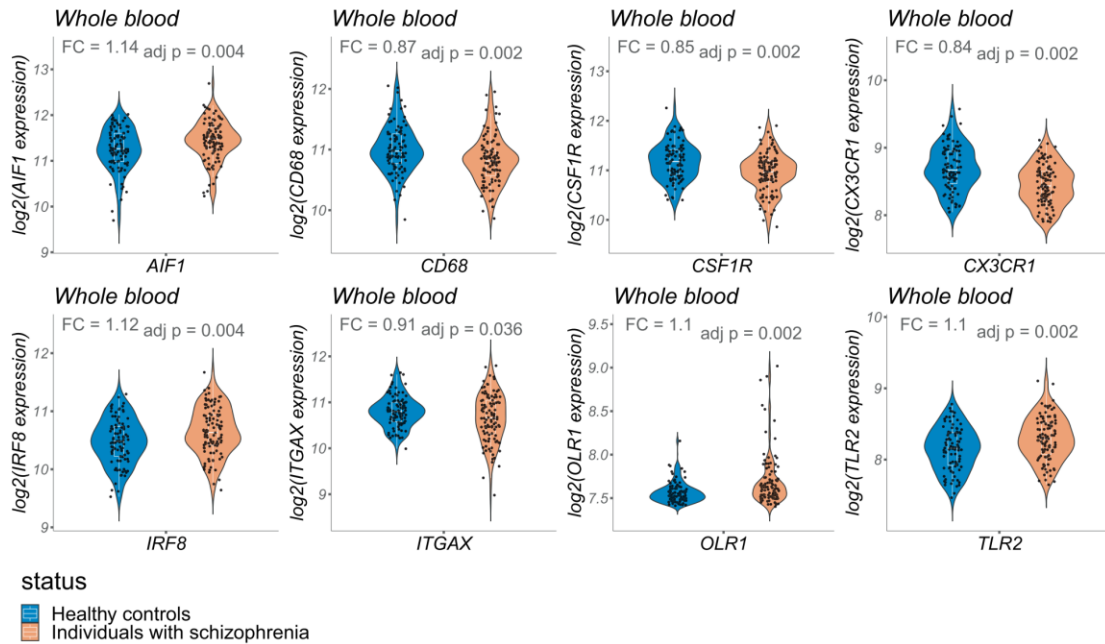
**Fig. 2** Differentially expressed genes in the postmortem brain samples of individuals with schizophrenia as compared with healthy controls. Shown are violin plots displaying gene expression distribution with overlaid box plots. For each gene, fold change (FC) represents the expression of the target gene in individuals with schizophrenia relative to that in healthy controls.

It should be noted that included datasets were collected from different subjects.

#### Differential expression analyses in postmortem brain tissues

Distinct transcription patterns of microglia genes were identified at the brain level in individuals with SZ compared with HCs. Individuals with SZ exhibited a set of genes significantly

underexpressed in the cerebellum (*AIF1*, *CD68*, *CSF1R*, *IRF8*, *ITGAX*), the associative striatum (*AIF1*, *CX3CR1*, *OLR1*), the hippocampus (*CX3CR1*) and parietal cortex (*OLR1*). No alterations were found in DLPFC, anterior prefrontal cortex, frontal cortex, and superior temporal cortex of individuals with SZ as compared with HCs. Results are depicted in Fig. 2 and fold-change and adjusted p-values are detailed in Supplementary Table 3.



**Fig. 3** Differentially expressed genes in the peripheral blood samples of individuals with schizophrenia as compared with healthy controls. Shown are violin plots displaying gene expression distribution with overlaid box plots. For each gene, fold change (FC) represents the expression of the target gene in individuals with schizophrenia relative to that in healthy controls.

When taking into account several covariates (e.g., age, sex, RIN, brain pH, postmortem interval) with ANCOVA analyses, all the findings remained, except for the underexpression of *AIF1* in the associative striatum (see Supplementary Table 4).

#### Differential expression analyses in peripheral tissues

In the whole blood, we found a decreased expression of *CD68*, *CSF1R*, *CX3CR1*, and *ITGAX* in individuals with SZ compared with HCs. Also, a significant overexpression of *AIF1*, *IRF8*, *OLR1*, and *TLR2* was observed in the whole blood. No significant differences in expression of microglia genes were observed in the PBMCs and skin fibroblasts. Results are depicted in Fig. 3 and fold-change and adjusted *p*-values are detailed in Supplementary Table 5.

When taking into account several covariates (e.g., age and sex) with ANCOVA analyses, all the findings remained, except for the *ITGAX* underexpression in the whole blood (see Supplementary Table 6).

#### Bayesian analyses

In postmortem brain tissues, using Bayesian analyses led to the same conclusions as frequentist statistics regarding the genes downregulated in SZ, with the exception of *AIF1* underexpression in the associative striatum of individuals with SZ compared with HCs (which was statistically significant in frequentist analysis whereas it was not possible to conclude in favor of the null or alternative hypotheses in Bayesian analyses). Notably, Bayesian analyses concluded with decisive evidence ( $BF_{10} > 100$ ) for the downregulation of *CX3CR1* in the hippocampus and of *OLR1* in the parietal cortex of individuals with SZ compared with HCs (see Supplementary Table 4).

In peripheral tissues, Bayesian and frequentist analyses yielded the same conclusions, with the exception of *ITGAX* underexpression in the whole blood of individuals with SZ compared with HCs for which Bayesian analyses did not allow to conclude in favor of

the null or alternative hypotheses. Noteworthy, Bayesian analyses concluded with decisive evidence ( $BF_{10} > 100$ ) for the underexpression of *CX3CR1* and *CSF1R* and overexpression of *OLR1* in the whole blood of individuals with SZ compared with HCs (see Supplementary Table 6).

#### DISCUSSION

In the present study we explored the expression of a pre-registered list of 10 genes from a core human signature of microglia in 8 different brain regions and in 3 peripheral tissues of individuals with SZ as compared with HCs. We observed altered expression patterns of the microglia-specific genes both in the brain and whole blood of individuals with SZ. The identified patterns were distinct between the different tissues. The present study allowed us to replicate and refine previous knowledge regarding SZ-associated microglial gene expression alterations as well as to expand such alteration to other brain regions and peripheral tissues.

#### Transcriptional alterations of microglia genes in brain tissues

First, we report altered transcriptional patterns of microglia genes in the cerebellum, associative striatum, hippocampus, and parietal cortex of individuals with SZ compared with HCs. Notably, in these 4 latter brain regions, all the identified transcriptional alterations were underexpressions. This is consistent with a recent meta-analysis reporting underexpression of microglia genes in the brain of individuals with SZ [15]. While meta-analytic results from Snijders et al. [15] were obtained by pooling expression data collected from 4 different brain regions (frontal, temporal, cingulate cortices and hippocampus), we analyzed separately postmortem datasets from different brain regions, allowing for more precise localization of effects. Thus, our findings expand the previously described underexpression of microglia genes to 3

additional brain regions relevant to SZ pathogenesis (namely the cerebellum, associative striatum and parietal cortex).

Among the explored brain regions, the cerebellum was characterized by the greatest number of underexpressed microglia genes (*AIF1*, *CD68*, *CSF1R*, *IRF8*, and *ITGAX*). Noteworthy, in the healthy brain cerebellar microglia is characterized by a unique profile [35]. These results are consistent with the growing body of literature involving the cerebellum in SZ pathogenesis [36–38]. Indeed, beside its role in motor coordination and balance, the cerebellum is also implied in cognitive and emotional functions [39, 40], and cerebellar dysfunctions have been linked to SZ symptoms such as hallucinations [41].

To our knowledge, it is the first time that transcriptional alterations of microglia-specific genes are reported in the associative striatum and hippocampus of individuals with SZ, although studies using animal models of SZ reported microglial alterations in these latter regions [42–45]. Remarkably, previous research suggested that striatal and hippocampal SZ-associated alterations involve dendritic spine loss, synaptic alterations and/or impaired neurogenesis [46–49], potentially through microglial dysfunction [50]. Our present results lend support to this hypothesis in two brain regions where adult neurogenesis events occur [51, 52].

Similarly, this is the first study to report *OLR1* underexpression in the parietal cortex of individuals with SZ. This finding is consistent with the correlation between microglial activity and altered cortical gray matter volume previously found in the parietal cortex of individuals with SZ [53].

However, we did not replicate previous reports of decreased expression of microglia genes in the frontal and temporal cortex of individuals with SZ [15, 54, 55]. The discrepancy may be accounted for by the heterogeneity of the samples' quality and demographic characteristics (such as differences in postmortem interval and sex distribution), sample size (our data were obtained from larger-sized samples as compared to the other studies) or techniques (we used microarray-derived data whereas these previous studies relied on quantitative real-time PCR techniques, it is therefore possible that alternative transcripts of the candidate genes were explored).

Overall, at the brain level, the consistency of the direction of the transcriptional alterations should be highlighted. Indeed, a recent systematic review investigating transcriptional alterations in SZ reported a high variability in the direction of the observed effect, with only few genes being consistently reported as over- or underexpressed across more than two or three studies [56]. Remarkably, in the present research, 3 genes (*AIF1*, *OLR1* and *CX3CR1*) showed the same direction of alteration in the analyzed brain samples. Most importantly, all the transcriptional alterations identified in 4 brain regions were underexpressions. In this light, our results suggest that brain underexpression of microglia genes may be considered as a candidate transcriptional signature for SZ. Furthermore, in individuals with SZ, the consistency of the direction of the transcriptional alterations contrasts with the heterogeneous results obtained using other microglia markers such as microglia activation, density, or morphology [13–16]. Our results thus strengthen the transcriptional analysis as a promising approach to explore SZ-associated microglia dysregulation.

Functionally, two alternative, non-exclusive hypotheses can be drawn regarding the identified underexpression patterns of microglia genes in the brain of individuals with SZ. As a first hypothesis, the observed transcriptional alterations may be related to the synaptic pruning impairment, which has been implicated in SZ pathogenesis [57]. Indeed, most of the candidate genes are involved in microglia key functions, such as “don't eat me signals” expressed by neurons which maintains microglia in a homeostatic state (for *CX3CR1*) [58], or microglial migration, adhesion and motility (for *CX3CR1*, *IRF8* and *AIF1*) [59–61]. Hence, in the brain of individuals with SZ, *CX3CR1*, *IRF8* and/or *AIF1*

underexpression may (i) either compromise the course of synaptic pruning by disrupting key microglial mechanisms [62] or (ii) reflect a regulatory attempt to counterbalance an excessive synaptic pruning in the brain of individuals with SZ [11, 63]. Alternatively, the identified transcriptional alterations may reflect a compensatory mechanism for neuroinflammation in the brain of individuals with SZ [64]. Consistently, animal models have involved several of our candidate genes (*CD68*, *CSF1R*, whose expression is necessary for microglia viability [65], *CX3CR1*, *AIF1*, *OLR1* and *ITGAX*) in inflammatory processes [66–72].

#### Transcriptional alterations of microglia genes in peripheral tissues

At the peripheral level, no changes were found in PBMCs and skin fibroblasts, although they are considered as promising surrogate tissues for the study of SZ pathogenesis [73, 74]. Nevertheless, transcriptional alterations were identified in the whole blood of individuals with SZ, showing the co-existence of 4 underexpressed genes (*CD68*, *CSF1R*, *CX3CR1*, *ITGAX*) and 4 overexpressed ones (*AIF1*, *IRF8*, *OLR1*, *TLR2*). Although both whole blood and PBMCs are derived from blood, PBMCs remain a subset of all blood cells. Thus, variations in gene expression are expected between those two compartments since they exhibit distinct specific expression profiles [75]. Furthermore, PBMCs and whole blood samples used in the present study were not derived from the same subjects. Therefore, the discrepant results may be attributed to differences in their collection, storage, and extraction methods, as well as in heterogeneity of demographic characteristics of the included datasets [76].

In individuals with SZ, while all the candidate genes differentially expressed at the brain level were also differentially expressed in the whole blood, the peripheral transcriptional alterations only partially reflected the cerebral ones. Indeed, *AIF1*, *IRF8* and *OLR1* showed opposite directions of change between the two levels. Furthermore, *TLR2* was overexpressed in the whole blood contrasting with the absence of change at the brain level. Different factors may explain brain and whole blood discrepancy in gene expression changes. First, in this study, blood and brain samples were not derived from the same subjects. Second, since gene expression is not expected to be uniform across all the different brain regions [77, 78], blood and brain gene expression correlation may differ depending on the brain region. Third, SZ pathogenesis may not be restricted to brain tissue as SZ is now considered as a “whole-body” disorder [79], with distinct alterations at the brain and peripheral levels.

Remarkably, besides *TMEM119* [34], all the differentially expressed genes in the whole blood of individuals with SZ are expressed by peripheral macrophages and/or involved in the production, differentiation, activation, function and survival of peripheral macrophages [80–87]. Thus, our whole blood results support a SZ-associated dysregulation of peripheral macrophages, which is consistent with a previous report [88] and with accumulating evidence of an immune dysregulation involvement in SZ pathogenesis [89]. In individuals with SZ, the coexistence of a brain microglia alteration together with a whole blood dysregulation of peripheral macrophages is reported here for the first time, although some previous studies paved the way to the present finding. Indeed, at the brain level, North et al. [88] reported dual microglia-perivascular macrophages alterations in the brain of individuals with SZ. At the peripheral level, using induced microglia-like cells from peripheral macrophages, Ormel et al. [90] suggested altered developmental pathways of microglia in individuals with SZ. Overall, while our brain-peripheral results support the model of SZ as a whole-body disorder [79], more research is needed to determine whether the whole blood transcriptional alterations identified only reflect a SZ-associated dysregulation of peripheral macrophages or can be considered as a peripheral transcriptional signature of dual brain microglia-peripheral macrophages alterations in individuals with SZ.

### Limitations

Interpretation of the present results might be affected by limiting factors.

First, brain and peripheral tissues were obtained from a total of 9 different and modest-sized samples of patients with SZ and healthy controls. These modest sample sizes inherently limit statistical power, leading to an increased risk of generating spurious findings. Although measures were taken to mitigate this limitation, such as focusing on a specific list of candidate genes and pre-registering the analysis plan, the constraint imposed by the small sample sizes remains a crucial consideration. Additionally, the unavailability of independent validation datasets within the GEO database prevented us from replicating our results. Future studies with larger sample sizes are thus warranted to corroborate and expand the current findings, thereby providing more robust insights into the gene expression patterns of microglia associated with SZ. Second, it should be highlighted that SZ is a highly heterogeneous disorder. Notably, recent research suggests that heightened inflammation may be characteristic of a specific subgroup within the SZ population [88, 91–93]. Interestingly, a recent study investigating the gene expression of four microglia markers found that patients with SZ who demonstrated a high inflammatory profile showed a down-regulation of CD68, in comparison to both patients with low inflammation and healthy controls [91]. However, due to the unavailability of clinical information and biomarker data within the GEO database, we were unable to perform an inflammatory profiling analysis to characterize these subgroups in our study. Therefore, future investigations should address the heterogeneity of SZ by exploring potential differential gene expression in these distinct subgroups.

Third, due to the limited availability of demographic information provided with GEO datasets, we could not investigate the influence of some potential confounding variables. For instance, we could not explore the effect of smoking or of suicide as a cause of death although such factors have been shown to influence gene expression [94, 95] and enhance proinflammatory processes [96, 97]. Similarly, the effect of antipsychotic treatment could not be evaluated, while it has been suggested that it may inhibit microglia activation [98].

Fourth, all the included datasets were acquired through microarray technology. Our results are thus subject to the methodological limitations that lie within the use of microarrays: (i) background hybridization limit gene expression measurement, especially for low abundance transcripts, (ii) probe performance may have led to specificity issues (through cross-hybridization and non-specific hybridization), (iii) only genes for which probes are designed can be explored.

Finally, brain expression data were obtained from postmortem cerebral samples composed of heterogeneous cell populations instead of isolating pure microglia. Despite this limitation, it is noteworthy that all the candidate genes were part of a core transcriptional signature of human microglia [21], as well as part of a microglia signature highly expressed in bulk brain tissues [22]. Nonetheless it is essential to conduct further investigations using high-throughput sequencing techniques such as single-cell RNA-seq technology [99], which can provide insights into the heterogeneity and diversity of microglia populations.

### Conclusion

Using 9 gene expression datasets, we report evidence of a widespread transcriptional alteration of genes from a core human microglia signature both in brain tissues and whole blood of individuals with SZ compared with HCs. In brain tissues, we expand and refine previous knowledge regarding underexpression of microglia genes in the cerebellum, associative striatum, hippocampus, and parietal cortex. Such alterations may be considered as a candidate transcriptional signature for SZ

disorders. At the peripheral level, we identified differential expression of the candidate genes in the whole blood of individuals with SZ. The dual brain-whole blood transcriptional alterations of microglia/macrophage genes identified in individuals with SZ support the model of SZ as a whole-body disorder and lend weight to the use of blood samples as a potential source of biological peripheral biomarkers. Subsequent investigations should thus focus on corroborating these findings within extensive population cohorts to enhance the robustness and generalizability of these conclusions.

### DATA AVAILABILITY

The data that support the findings of this study are openly available in Gene Expression Omnibus (NCBI) at <https://www.ncbi.nlm.nih.gov/geo/>, reference numbers GEO: GSE53987, GSE17612, GSE35977, GSE35974, GSE62191, GSE21935, GSE27383, GSE62333, GSE38484.

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#### AUTHOR CONTRIBUTION

Concept and design: All authors. Statistical analysis: AMF, RR. Interpretation of data: AMF, ECI, RR. Drafting of the manuscript: AMF, RR. Critical revision of the manuscript for important intellectual content: All authors. We would like to thank Jasmine Dumas and Garrett Dancik from the Department of Computer Science at Eastern Connecticut State University for the development of shinyGEO application and for their help in using the application.

#### FUNDING

AMF was supported by the Fondation Pierre Deniker. EF was supported by the Fondation de France. GS was supported by the Agence Nationale de la Recherche [grant number ANR-19-CE37-0012-01] and the Fondation NRJ-Institut de France. RR was supported by the Fondation FondaMental and the Vinatier Hospital [grant number CSR-H11].

#### COMPETING INTERESTS

The authors declare no competing interests.

#### ADDITIONAL INFORMATION

**Supplementary information** The online version contains supplementary material available at <https://doi.org/10.1038/s41398-023-02677-y>.

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## CONCLUSION ET PERSPECTIVES

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Dans cette thèse nous nous sommes intéressés aux corrélats cérébraux liés à la perception émotionnelle, en nous demandant si ces corrélats pouvaient être utilisés en tant qu'endophénotypes de la schizophrénie. Pour tester cette hypothèse, nous avons étudié la présence d'anomalies cérébrales chez des individus sains considérés à risque accru de développer une schizophrénie. Notre attention s'est principalement portée sur les apparentés de patients atteints de schizophrénie, qui partagent une part significative du patrimoine génétique avec leur frère ou sœur atteint(e) de schizophrénie. Cette approche nous permet d'étudier les mécanismes de vulnérabilité génétique, connus pour jouer un rôle majeur dans le développement de la schizophrénie. En effet, bien qu'une partie de l'héritabilité génétique de la schizophrénie reste à élucider, les études menées sur des jumeaux suggèrent que celle-ci pourrait expliquer jusqu'à 80 % du risque de développer la maladie (Hilker et al., 2018). De plus, l'étude des apparentés sains permet également de minimiser les effets confondants liés à la maladie elle-même ou aux traitements médicamenteux.

Tout d'abord, nous avons adopté une approche méta-analytique pour faire le point sur les connaissances actuelles concernant l'activation cérébrale chez les individus à risque de schizophrénie lors du traitement émotionnel (Chapitre I). Afin de pouvoir généraliser nos conclusions et augmenter la puissance statistique en incluant un plus grand nombre d'études, nous avons examiné trois types de populations considérées à risque, souvent étudiées dans la littérature : les apparentés, les sujets à haut risque clinique, et les individus présentant des traits de schizotypie élevés. Nous avons rassemblé les cartes statistiques non seuillées du cerveau entier issues d'études en IRMf comparant ces populations à des sujets contrôles pour étudier l'activation cérébrale en réponse à des stimuli émotionnels par rapport à des stimuli neutres, comme cela est couramment fait dans la littérature, ou à une condition contrôle. Nos résultats n'ont pas montré de différences d'activation par rapport aux sujets contrôles, y compris dans des régions limbiques comme l'amygdale, fortement impliquée dans le traitement émotionnel. Toutefois, des difficultés dans la reconnaissance émotionnelle sont observées au niveau comportemental, comme montré par des méta-analyses à la fois chez les apparentés (Lavoie et al., 2013; Martin et al., 2015), ainsi que chez des individus à risque

clinique (Lee et al., 2015), suggérant que ces anomalies pourraient être sous-tendues par d'autres dysfonctionnement cérébraux. En particulier, puisque les émotions sont traitées par un ensemble complexe de structures interconnectées, il est possible que l'activité coordonnée des régions cérébrales reflète mieux ces anomalies plutôt que l'activité isolée au sein de régions spécifiques.

Nous avons ensuite mené une deuxième méta-analyse, en adoptant une approche similaire à la précédente, mais cette fois en analysant les activations cérébrales en réponse à des visages neutres chez les apparentés de patients atteints de schizophrénie (Chapitre II). Cet intérêt découle des travaux antérieurs qui ont montré que ces stimuli ne sont souvent pas perçus comme réellement neutres par les patients vivant avec une schizophrénie, étant fréquemment interprétés comme émotionnels. Ce phénomène est accompagné d'une hyperactivation des régions émotionnelles du système limbique, en particulier de l'amygdale. Nous avons montré qu'à l'inverse, les apparentés présentent des hypoactivations des régions limbiques, pouvant suggérer la présence de facteurs protecteurs. Cette interprétation est cohérente avec des études récentes avec des échantillons de grande taille ainsi que des méta-analyses, qui ne montrent pas de difficultés dans la reconnaissance des stimuli neutres chez les apparentés (Allott et al., 2015; Andric et al., 2016; Fett et al., 2013; Martin et al., 2020). Bien que les apparentés au premier degré partagent environ la moitié de leurs gènes avec leur frère ou sœur atteint(e), d'autres facteurs génétiques, potentiellement liés à leur patrimoine génétique restant, pourraient avoir un rôle protecteur. Nous avons également étendu aux apparentés des patients vivant avec une schizophrénie les mises en garde concernant l'utilisation de ces stimuli comme comparateur dans les études en IRMf, conformément aux recommandations déjà soulevées dans des études antérieures chez les patients (Anticevic et al., 2012; Dugré et al., 2019).

À la lumière des observations faites dans les Chapitres I et II, nous avons mené une étude en IRMf auprès de 37 patients atteints de schizophrénie, 39 apparentés et 42 sujets contrôles (Chapitre III). L'objectif était d'examiner l'activation et la connectivité cérébrale lors du traitement de stimuli émotionnels, en nous concentrant sur des visages exprimant des émotions négatives. Ces stimuli sont régulièrement identifiés dans la littérature comme ceux présentant les preuves les plus solides d'un déficit dans le continuum de la schizophrénie (Gao

et al., 2021; Martin et al., 2020). De plus, nous avons utilisé une condition contrôle appropriée, plutôt que des visages neutres. Nos résultats ont montré que, dans la majorité des régions cérébrales, les activations étaient comparables entre les patients et les apparentés par rapport aux sujets contrôles. Nous avons également mis en évidence que, par rapport aux sujets contrôles, le cortex somatosensoriel droit était une région dans laquelle tant les apparentés que les patients montraient des réductions d'activation lors de la présentation de visages négatifs par rapport à la condition contrôle. Cela suggère l'existence d'un dysfonctionnement cérébral commun entre les patients et leurs apparentés, tout en remettant en question les anomalies d'activation de l'amygdale traditionnellement observées lorsque des stimuli neutres sont utilisés comme comparateurs. Enfin, nous avons observé que, par rapport aux sujets contrôles, chez les apparentés l'amygdale droite était plus fortement connectée au cuneus droit. Ce résultat souligne que l'activation cérébrale ne permet pas de saisir toutes les nuances du traitement émotionnel dans la schizophrénie. En outre, il suggère qu'une connectivité accrue entre l'amygdale droite et le cuneus droit pourrait sous-tendre un mécanisme compensatoire chez les apparentés, facilitant ainsi la gestion des informations émotionnelles en améliorant l'intégration entre les circuits émotionnels et visuels.

Enfin, partant du principe que les endophénotypes sont des marqueurs intermédiaires entre le niveau génétique et les manifestations cliniques, nous nous sommes également intéressés à la composante génétique de la schizophrénie. En particulier, nous avons cherché à étudier le rôle de la microglie, en raison de son implication centrale dans l'inflammation, l'élagage synaptique, l'interaction entre vulnérabilité et stress, et possiblement le traitement émotionnel -des mécanismes clés dans le développement et la progression de la schizophrénie. Nous avons cartographié les anomalies d'expression génétique de la microglie, montrant une sous-expression microgliale dans diverses régions cérébrales, accompagnées par des sous- ou sur-expressions au niveau périphérique. Nous avons souligné l'importance d'étudier dans de futures études si ces anomalies sont déjà présentes chez les apparentés des patients, afin de déterminer si elles pourraient servir des marqueurs précoces de vulnérabilité génétique à la schizophrénie.

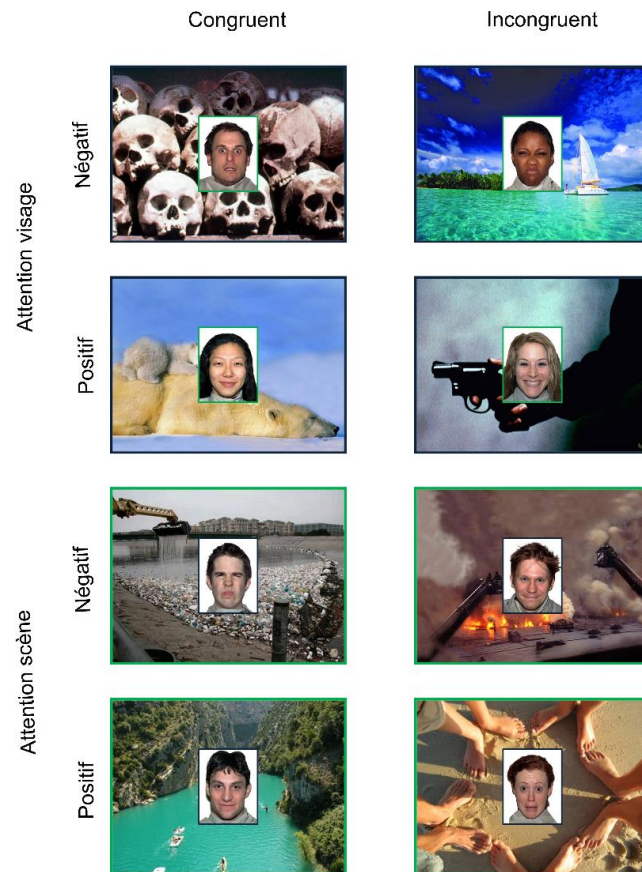
Dans les prochains paragraphes, nous examinerons les pistes de recherche potentielles pour les études futures à la lumière de ces résultats.

## Est-il nécessaire d'explorer davantage les différentes facettes du traitement émotionnel pour consolider un endophénotype robuste ?

À la lumière des résultats de notre méta-analyse sur les stimuli émotionnels chez les individus à risque de schizophrénie (*Article #1, Fiorito et al., Biol Psychiatry, 2022*), et en tenant compte des recherches existantes sur le traitement émotionnel dans cette pathologie, nous avons choisi, dans notre étude en IRMf (*Article #3, Fiorito et al., In Prep*), d'exploiter la partie de la tâche qui s'alignait le mieux avec la littérature existante. Cela nous a permis d'explorer les corrélats cérébraux du traitement émotionnel, tout en établissant des parallèles avec cette littérature précédente. Cependant, il est important de souligner que la tâche que nous avons employée présente l'avantage d'étudier la perception émotionnelle à un niveau plus sophistiqué et écologique par rapport aux tâches précédemment utilisées dans la littérature, en superposant des visages émotionnels à des contextes également émotionnels. Ainsi, cette approche permet de couvrir plusieurs aspects du traitement émotionnel, en manipulant spécifiquement trois facteurs distincts : la valence émotionnelle (avec des stimuli positifs et négatifs), le niveau attentionnel (les participants se concentrent soit sur le visage, un stimulus saillant, soit sur la scène, en arrière-plan et demandant plus d'attention), ainsi que la congruence (la valence émotionnelle du visage et de la scène peut être similaire ou opposée).

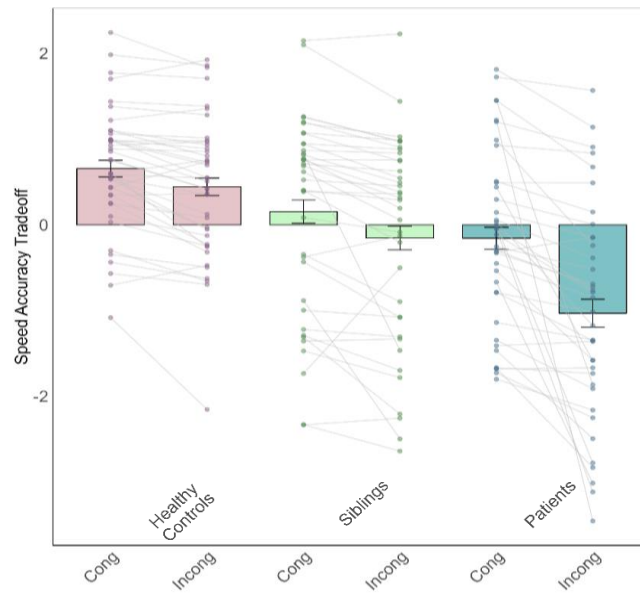
Afin d'exploiter tout le potentiel de la tâche, nous avons également réalisé des analyses comportementales en employant une analyse de la variance (ANOVA) à deux facteurs, avec un facteur inter-groupe (sujets contrôles, apparentés, patients) et trois facteurs intra-groupe (valence, attention, congruence). Comme pour les analyses précédentes, nous avons utilisé le « *Balanced integration Score* » (Liesefeld & Janczyk, 2019), qui permet d'étudier le compromis entre la vitesse et la précision. Comme attendu, nous avons observé un effet principal du groupe, ainsi qu'un effet principal pour chaque facteur de la tâche : valence, attention, congruence. De façon intéressante, ces analyses ont montré une **interaction entre le groupe et la congruence**, indiquant que l'effet de la congruence (c'est-à-dire la différence de performance à la tâche entre les stimuli congruents et incongruents) varie selon le groupe (voir Figure 9 pour une représentation des stimuli de la tâche). Nous avons observé un pattern endophénotypique, dans lequel il y a une faible différence entre les stimuli incongruents et congruents chez les sujets contrôles, une différence importante chez les patients, et une

différence intermédiaire chez les apparentés (voir Figure 9 pour la représentation des résultats sous forme de diagramme à barres). Ces résultats suggèrent donc que l'efficacité du traitement émotionnel dans un contexte avec des stimuli incongruents pourrait constituer un endophénotype intéressant.



**Figure 9**

*Représentation des stimuli de la tâche « variable attention and congruency task » (VAAT ; Comte et al., 2016), qui manipule trois facteurs : la valence (stimuli positifs ou négatifs), l'attention (aux visages ou aux scènes) et la congruence (stimuli congruents ou incongruents).*



**Figure 10**

*Diagramme en barres illustrant les scores du compromis vitesse-précision (mesurés par le « Balanced Integration Score », BIS), pour l'interaction entre les groupes et les conditions de la congruence (stimuli congruents, incongruents). La hauteur de chaque barre représente le score moyen de BIS du groupe, avec des barres d'erreur représentant  $\pm 1$  erreur standard de la moyenne. Les données individuelles sont affichées sous forme de points, et des lignes grises relient les performances du même participant à travers les conditions. La pente de ces lignes reflète le changement de score BIS de la condition congruente à la condition incongruente au sein des participants.*

Le Consortium on the Genetics of Schizophrenia a proposé d'utiliser le *Penn recognition face test*, dans lequel les participants sont exposés à des visages exprimant différentes émotions, pour mesurer les endophénotypes émotionnels dans la schizophrénie (Gur et al., 2007). Néanmoins, la perception émotionnelle à laquelle nous sommes exposés au quotidien est nettement plus complexe que la simple présentation de visages exprimant des émotions. Les difficultés liées à la perception émotionnelle pourraient s'accroître lorsque l'on étudie des niveaux plus élaborés du traitement émotionnel. L'exploration de ces aspects plus complexes pourrait permettre de valider des endophénotypes présentant une pertinence clinique accrue.

L'utilisation d'une **tâche plus complexe et écologique, telle que la VAAT**, suggère que la congruence émotionnelle pourrait être un facteur pertinent dans la recherche d'endophénotypes. De façon intéressante, ces résultats comportementaux mettent en lumière une difficulté particulière dans la schizophrénie face à l'**ambiguïté émotionnelle**. Cette observation s'inscrit de manière cohérente dans le cadre des anomalies cérébrales observées dans le continuum de la schizophrénie en réponse à des stimuli neutres, comme discuté dans le Chapitre II. Les visages neutres, en particulier, peuvent être considérés comme des stimuli sociaux intrinsèquement ambigus. Leur interprétation dépend fortement du contexte et des expériences individuelles, ce qui les rend particulièrement sensibles aux biais de perception.

Une prochaine étape consistera à explorer les corrélats cérébraux associés à ce modèle spécifique, afin de déterminer si les anomalies comportementales observées lors d'une incongruence émotionnelle sont dues à des dysfonctionnements cérébraux et d'identifier d'éventuels endophénotypes potentiellement plus robustes.



## Les endophénotypes permettent-ils réellement de surmonter la complexité génétique ? Vers une approche multi-dimensionnelle

L'étude des endophénotypes est particulièrement pertinente dans le cadre des maladies polygéniques, où il est difficile d'établir des liens directs entre les gènes et le comportement. Dans ce contexte, une étape supplémentaire dans notre compréhension des mécanismes contribuant à l'étiopathogénie de la schizophrénie consiste à éclairer la composante génétique susceptible de conduire à la formation de systèmes cérébraux dysfonctionnels. Ainsi, pour une maladie complexe comme la schizophrénie, il est essentiel d'adopter une approche « **multi-dimensionnelle** », permettant une compréhension globale de la pathologie.

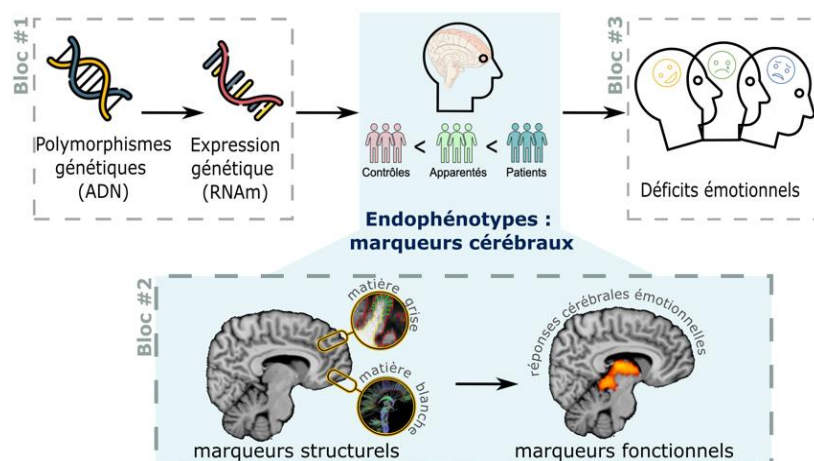
Apporter cette nuance constitue l'un des objectifs de l'étude présentée dans le Chapitre III. En effet, les résultats d'imagerie fonctionnelle discutés dans ce chapitre s'inscrivent dans un projet plus vaste, incluant également des séquences d'imagerie structurelle et des prélèvements sanguins. Ce projet vise à examiner comment certaines variations génétiques conduisent au développement de structures cérébrales anormales, entraînant à leur tour un dysfonctionnement des réseaux neuronaux, responsables des déficits comportementaux observés. En effet, il a par exemple été proposé que des altérations génétiques des gènes liés à la microglie et au complément, les acteurs principaux de l'élagage synaptique, pourraient amener à un élagage excessif des synapses qui se refléterait par un assouplissement de l'épaisseur corticale (Selemon & Goldman-Rakic, 1999). De plus, il est souvent proposé que les anomalies structurelles influencent et déterminent le fonctionnement des circuits cérébraux (Fornito & Bullmore, 2015).

Une perspective future consistera à élaborer un modèle intégrant ces différents domaines complémentaires (biologie moléculaire, neuroimagerie structurelle et fonctionnelle, et comportement). Cela permettrait de tester si les apparentés présentent des marqueurs cérébraux intermédiaires entre ceux des patients et des sujets contrôles, qui peuvent être prédit par les patterns transcriptomiques. A cette fin, nous collaborons avec des bioinformaticiens pour appliquer des méthodes de « *Sparse Generalized Canonical Correlation Analysis* » (Tenenhaus et al., 2014), un **modèle multiblocs** qui permet de relier des ensembles de données hétérogènes (dits « blocs »), et de faire émerger, dans chaque bloc, un nombre

restreint de variables jouant un rôle clé à la fois au sein de leur bloc et dans les relations inter-blocs (voir Figure 11 pour une représentation du modèle multiblocs).

Afin d'inclure des données sanguines dans ce modèle, en particulier celles liées à l'expression génétique, j'ai effectué un séjour de deux mois au laboratoire de l'Institut de Neurosciences de la Timone à Marseille, sous la supervision du Dr. El Chérif Ibrahim. Durant ce séjour, j'ai isolé et extrait l'ARN total à partir des prélèvements sanguins de la cohorte de patients atteints de schizophrénie, apparentés sains et sujets contrôles présentée dans le Chapitre III (*Article #3, Fiorito et al., In Prep*). Pour cela, nous nous sommes servis du protocole du kit « *LeukoLOCK™ Total RNA Isolation System* » qui permet de purifier l'ARN des globules blancs du sang périphérique par des étapes de lyse des cellules, extraction phénolique acide, précipitation alcoolique et rétention sur colonne avant des lavages et une élution dans de l'eau ultrapure. Par ailleurs l'ARN a été traité à la ADNase pour éliminer toute trace d'ADN génomique résiduel. Ensuite, le séquençage de l'ARN a été réalisé par une entreprise privée.

Une étape future consistera à intégrer les patterns transcriptomiques ainsi dérivés dans un modèle incluant également des marqueurs structurels et fonctionnels, afin de dresser un portrait de la schizophrénie favorisant une compréhension multidimensionnelle de la maladie.



**Figure 11**

*Schéma du modèle multiblocs, permettant de prendre en compte une conception structurelle décrivant les relations entre des blocs (ici génomique → neuroimagerie → comportement) et d'identifier dans chaque bloc un sous-groupe de variables actives dans le lien avec les autres blocs, émergeant ainsi comme centrales dans la compréhension de la maladie.*

## Pourquoi y a-t-il une difficulté à valider des endophénotypes cliniquement pertinents dans la psychiatrie ?

Les biomarqueurs, en particulier les endophénotypes, promettent de faciliter la détection précoce du risque de développer la maladie, ainsi que d'aider au pronostic et à l'identification de cibles pertinentes pour les interventions thérapeutiques (Iacono, 2018), telles que les techniques de stimulation cérébrale (Brunelin et al., 2022). Ainsi, dans certaines disciplines, l'utilisation des biomarqueurs est couramment intégrée à la pratique clinique. Par exemple, en oncologie, cela a révolutionné le diagnostic ainsi que la prise en charge des patients (Zhou et al., 2024). En revanche, en psychiatrie, le diagnostic repose exclusivement sur l'observation des symptômes. Les manuels de classification des troubles psychiatriques, comme le DSM, définissent une liste de symptômes, et pour qu'un diagnostic soit posé, une personne doit en présenter un certain nombre. Cette approche nosologique, basée sur un nombre minimal de caractéristiques issues d'une liste plus longue, entraîne inévitablement une grande hétérogénéité. Par exemple, pour le trouble dépressif majeur il existe 227 façons différentes de répondre aux critères diagnostiques, et il est possible que deux patients diagnostiqués avec un trouble dépressif majeur n'aient aucun symptôme en commun (Zimmerman et al., 2015).

De plus, d'autres facteurs contribuent à expliquer l'importante **hétérogénéité** des troubles psychiatriques (Wolfers et al., 2018). En plus d'une hétérogénéité **clinique** on observe également une hétérogénéité **biologique**, dans le sens que différentes prédispositions biologiques peuvent converger dans les symptômes. Par exemple, comme nous l'avons vu dans l'introduction, le caractère polygénique de la schizophrénie fait qu'il n'y a pas un profil génétique clair et unique qui est considéré à risque, mais il s'agit plutôt d'une vulnérabilité, plus ou moins importante selon l'individu. Enfin, il y a également une hétérogénéité **environnementale**, signifiant que différents facteurs environnementaux peuvent intervenir et influencer si l'individu va ou non développer une maladie psychiatrique.

Cette variabilité réduit notre capacité à discerner des patterns cohérents de différences entre les groupes. Plus important encore, elle empêche de traduire ces patterns dans les pratiques cliniques, afin de faire progresser la **psychiatrie de précision**, une approche innovante qui vise à proposer des stratégies de traitement et de prévention sur mesure.

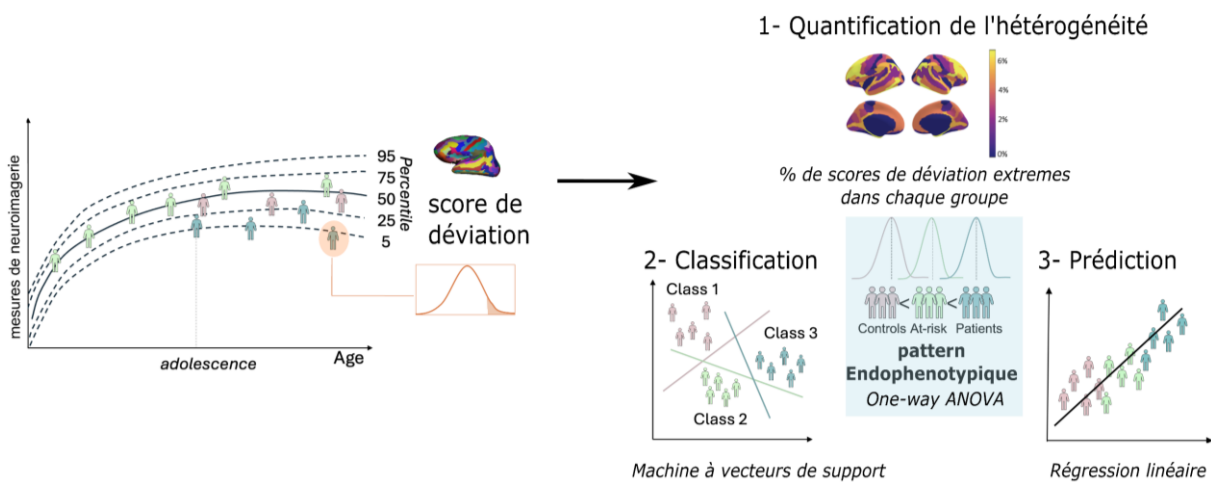
Certaines initiatives, telles que les RDoCs discutées dans l'introduction, proposent de nouveaux cadres de recherche, basé sur l'adoption d'une approche **transdiagnostique** et multidimensionnelle qui prend en compte les aspects biologiques et comportementaux. Il a également été suggéré que les endophénotypes pourraient jouer un rôle clé dans cette démarche. Bien que les endophénotypes aient été initialement conçus pour être spécifiques à un trouble, il est désormais reconnu que les comorbidités dans les troubles psychiatriques sont la règle plus que l'exception, et que les symptômes présentent un fort caractère transdiagnostique. A titre d'exemple, les difficultés dans la reconnaissance d'émotions ont été observées également chez les patients vivant avec un trouble bipolaire et une dépression (Kohler et al., 2011), ainsi que chez ceux atteints d'un trouble autistique (Leung et al., 2022), et chez leurs proches au premier degré (Hu et al., 2018; Işık Ulusoy et al., 2020; Kjærstad et al., 2023). Même si toutes les personnes atteintes d'un trouble ne présentent pas nécessairement le même endophénotype, la présence d'un endophénotype peut indiquer une vulnérabilité, sans être exclusivement liée à un trouble spécifique (Iacono, 2018). Ainsi, les endophénotypes pourraient aider à identifier des individus plus vulnérables, en ne se basant pas uniquement sur des critères cliniques. Par exemple, ils pourraient permettre de repérer des personnes à **risque endophénotypique**, facilitant ainsi l'identification des facteurs environnementaux et d'autres éléments de risque qui interagissent avec ces mécanismes endophénotypiques et contribuent au développement de la pathologie (Iacono, 2018).

Enfin, il a été souligné que la reconnaissance de ces limites et la nécessité d'aborder la complexité et l'hétérogénéité observées en psychiatrie ne sont pas accompagnées d'un changement dans les stratégies d'analyse des données (Marquand et al., 2019). Dans ce contexte, des approches méthodologiques innovantes ont émergé, telles que les **modèles normatifs**. Cette approche se distingue de la méthodologie traditionnelle de cas-témoins, et remet en question la présupposition que les patients et les témoins sains constituent des entités homogènes bien définies (Marquand et al., 2016). Comparable aux courbes de croissance qui juxtaposent la taille d'un enfant par rapport à la distribution normative de la taille pour un âge particulier, la modélisation normative permet de caractériser les corrélats cérébraux par rapport à une norme standard à un âge spécifique. Ainsi, cette approche permet de quantifier et de caractériser au niveau individuel la manière dont différents individus s'écartent du schéma moyen attendu (à travers ce qu'on appelle les scores de déviation). Il est

important de noter que cette approche ne nécessite pas un chevauchement des anomalies dans les mêmes zones cérébrales chez les participants, ni même un schéma de déviation unique et cohérent, ce qui permet d'accommoder l'hétérogénéité des profils (Voir la Figure 12 pour un schéma illustrant les modèles normatifs et leurs applications).

Des recherches précédentes s'appuyant sur cette approche ont souligné que l'utilisation des approches basées sur la division cas-témoins obscurcit des variations interindividuelles significatives chez les patients atteints de schizophrénie (Wolfers et al., 2018, 2021), soulevant des doutes quant à l'efficacité de l'étude d'un « patient moyen ». En revanche, une approche basée sur les modèles normatifs permet d'incorporer ces variations, offrant ainsi un cadre pour la psychiatrie de précision. Il a été montré que l'utilisation de ces approches permettait de classer les patients vivant avec une schizophrénie avec une précision beaucoup plus forte que l'utilisation d'approches classiques cas-témoins (Rutherford et al., 2023).

Les études futures devront explorer les bases neurobiologiques des déficits émotionnels le long du continuum de la schizophrénie en utilisant la modélisation normative, dans le but d'identifier des marqueurs endophénotypiques pouvant expliquer la variabilité individuelle, susceptibles d'avoir une utilité clinique accrue.



**Figure 12**

*Schéma illustrant les modèles normatifs et leurs applications. Ces modèles permettent d'établir des scores de déviation, quantifiant ainsi, au niveau du sujet, la manière dont les individus s'écartent du schéma attendu. Ces scores peuvent être utilisés pour mesurer l'hétérogénéité entre les individus et promettent d'améliorer la classification et la prédiction des troubles psychiatriques.*

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## ANNEXES

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**Travail complémentaire à la thèse** : Article sur l'aversion à la perte dans les contextes monétaire et alimentaire

**Matériel complémentaire de l'Article #1**

**Matériel complémentaire de l'Article #2**

**Matériel complémentaire de l'Article #4**

## **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 14<sup>th</sup> March 2008 and 7<sup>th</sup> 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.

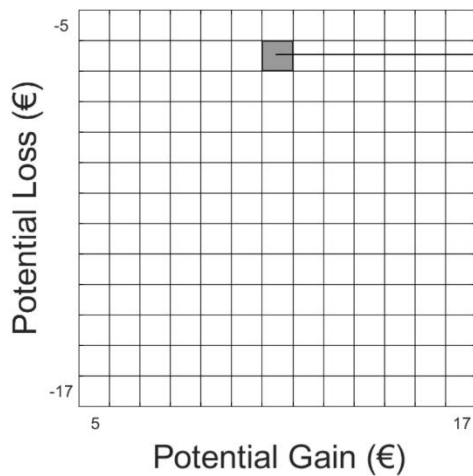
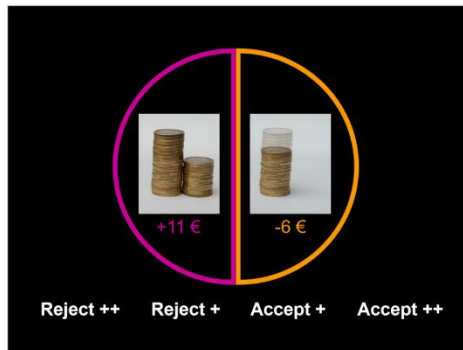
Sixty-seven healthy volunteers were recruited through advertisement. The following inclusion criteria were used: aged between 18 and 45 years old, female, fluent French speaker, no history of eating disorders, no psychological or neurological disorder, no current psychotropic medication, and normal or 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.

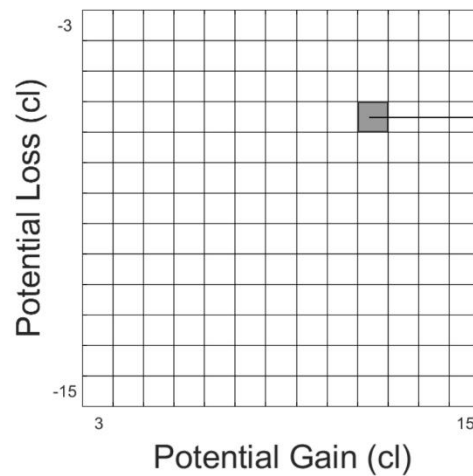
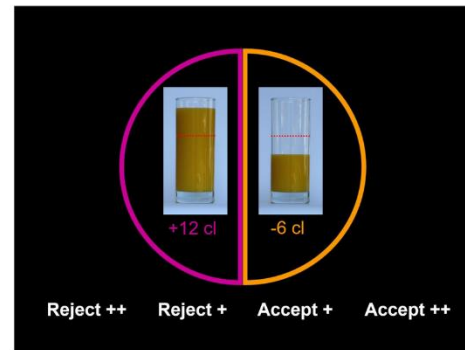
## Experimental tasks

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  $\beta_{\text{gain}}$  and  $\beta_{\text{loss}}$  (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,  $p_{\text{Gain}}$  is the gain probability and  $p_{\text{Loss}}$  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  $\lambda$ . 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 ( $\mu$ ) 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  $\mu$  reflect increasing consistency in choice behavior, with positive values of  $\mu$  reflecting higher gamble acceptance with higher gain and lower loss value, and vice versa for negative values of  $\mu$ .

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

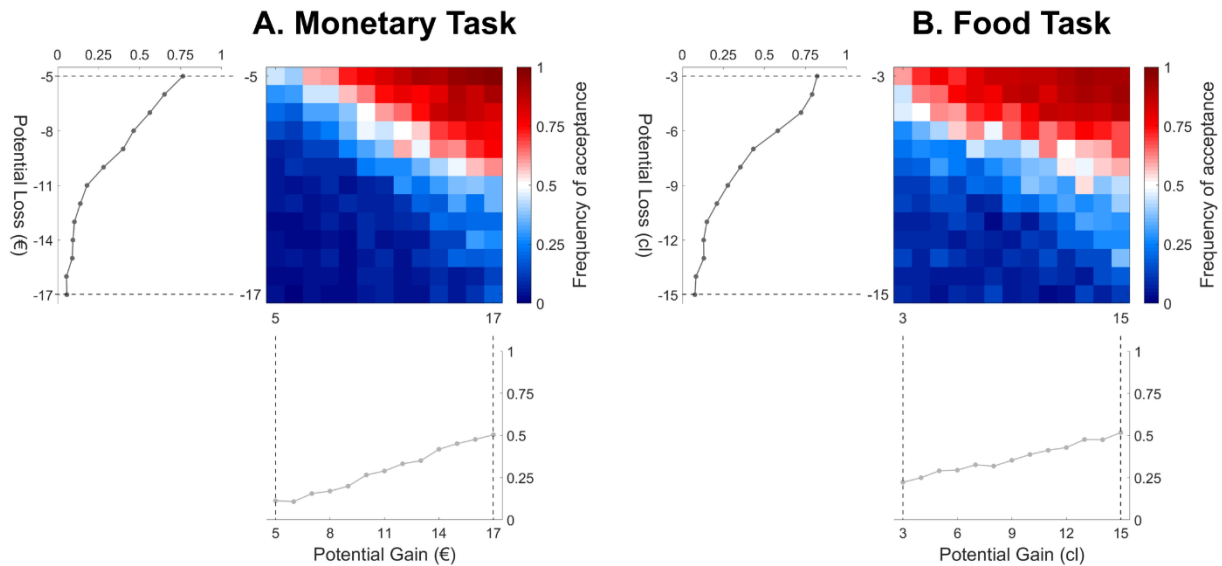
The mean subjective motivation ratings (measured by means of a 5-point Likert scale and averaged across the pre-task and post-task ratings) were respectively 4.22 (SD = 0.81) in the monetary domain and 3.68 (SD = 0.87) in the food domain.

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].

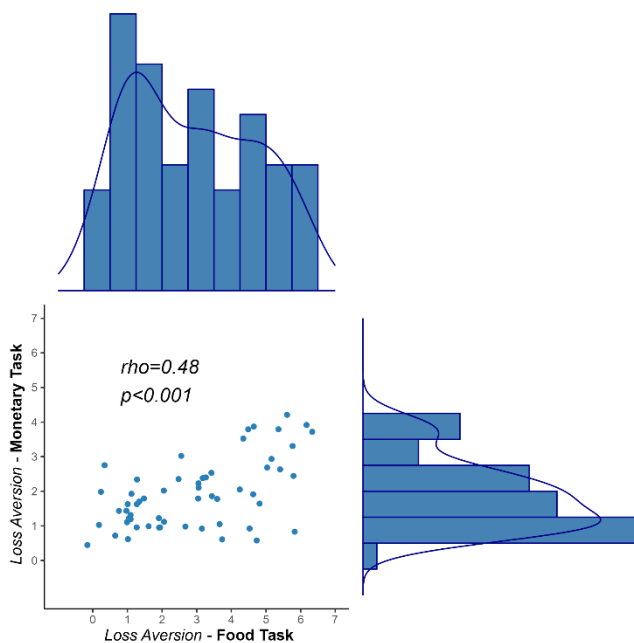
|               | Monetary Task                  |                                      | Food Task                      |                                      |
|---------------|--------------------------------|--------------------------------------|--------------------------------|--------------------------------------|
|               | Group mean<br>(standard error) | Group median<br>(standard deviation) | Group mean<br>(standard error) | Group median<br>(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.

## **Acknowledgments**

**Funding:** the ENDANO cohort (D428) was funded by the Programme Hospitalier de Recherche Clinique. The research leading to these results received funding from the MILDT/INSERM (MIL0805) to J.-C.D. G.S. was funded by a PhD fellowship from the French Ministry of Research and the Fondation pour la Recherche Médicale (FDT20091217744). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

**Competing interests:** PG has received financial support during the last 5 years from Janssen, Lundbeck, Otsuka. All other authors report no relevant financial or non-financial interests to disclose.

**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.

**Additional contributions:** We would like to thank Payam Piray, Princeton Neuroscience Institute, Princeton University, Princeton, NJ USA, for his help with the computational and behavioral modeling toolbox.

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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:**

- Supplementary Methods
- Supplementary Table S1
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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  |
|-------------------------|--------|--|--|
| <b>TITLE</b>            |        |  |  |
| Title                   | 1      | Identify the report as a systematic review.  | Title  |
| <b>ABSTRACT</b>         |        |  |  |
| Abstract                | 2      | See the PRISMA 2020 for Abstracts checklist.   | Abstract   |
| <b>INTRODUCTION</b>     |        |  |  |
| 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   |
| <b>METHODS</b>          |        |  |  |
| 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> )           |
| <b>RESULTS</b>                |        |   |  |
| 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> )                                |
| <b>DISCUSSION</b>             |        |  |   |
| 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  |
| <b>OTHER INFORMATION</b>                       |        |  |   |
| 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 |

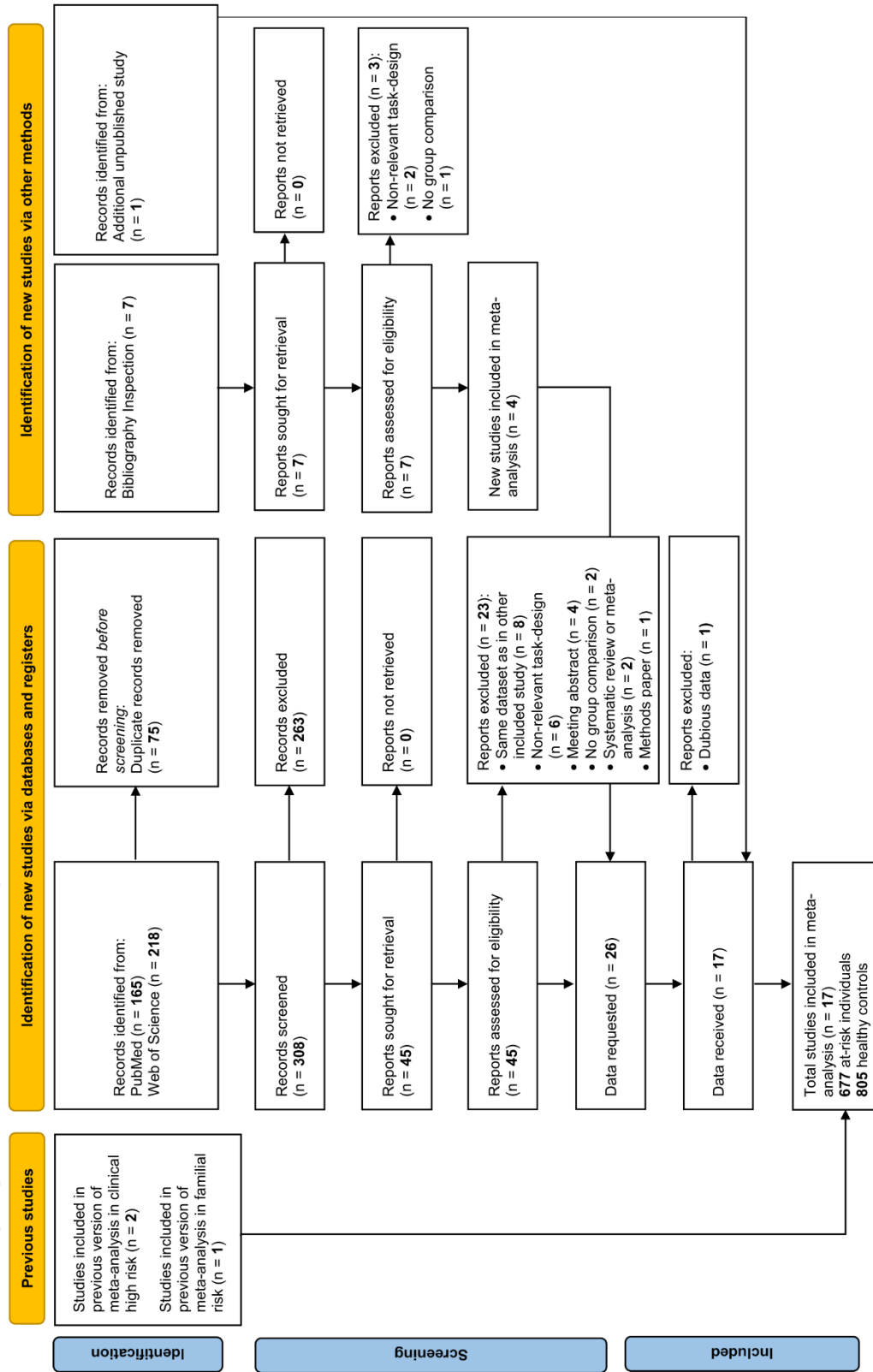
| <b>Brain region</b>                     | <b>Hemisphere</b> | <b>MNI (x,y,z)</b> | <b>SDM-Z</b> |
|---|-------------------|--------------------|--------------|
| Amygdala                                | Right             | 22,-4,-18          | 3.299        |
| <i>Healthy controls - deactivations</i> |                   |                    |              |
| 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 |

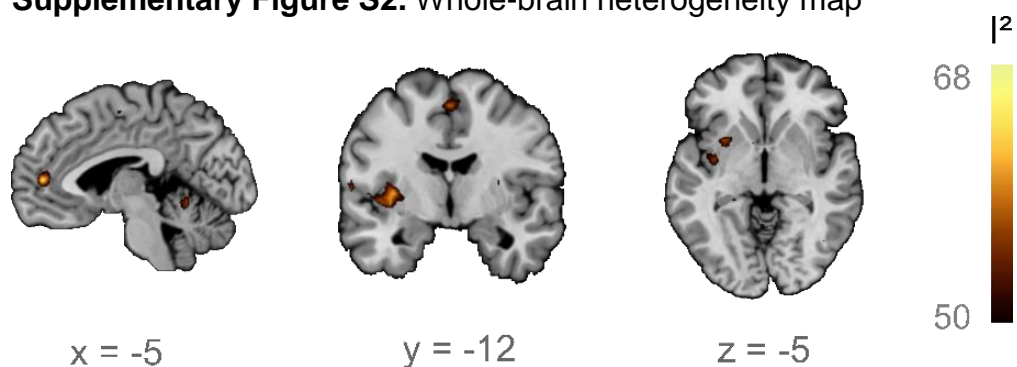
$p_{TFCE} < 0.05$



**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.*

**Contents:**

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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 faces<sup>1-12</sup>
- 11 studies used non-relevant task design (1 structural magnetic resonance imaging<sup>13</sup>, 2 non-visual stimuli<sup>14,15</sup>, 2 resting state<sup>16,17</sup>, 6 studies employed scenes or stories instead of faces<sup>18-23</sup>)
- 7 were conference abstracts<sup>24-30</sup>
- 7 studies employed the same dataset as in another included study<sup>31-37</sup>
- 6 studies were systematic reviews or meta-analyses<sup>38-43</sup>
- 6 study did not include a group of first-degree relatives<sup>44-49</sup>
- 1 study was a method paper<sup>50</sup>

### *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<sup>51,52</sup>.

**Table S1. Quality assessment checklist** adapted from Zheng et al., 2018<sup>53</sup>. 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.

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**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

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**Category 2: Methodology and reporting**

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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 <sup>54</sup> | 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 <sup>55</sup>   | 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 <sup>56</sup>     | To investigate implicit emotion processing in schizophrenia                                       | Abnormal brain activity to fearful and neutral faces in first-degree relatives   | 11            |
| Pirnia et al., 2015 <sup>57</sup>   | To investigate associative memory in schizophrenia  | Abnormal brain activity to successful encoding in patients with schizophrenia  | 11.5          |
| Quarto et al., 2018 <sup>58</sup>   | 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 <sup>59</sup>   | 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 <sup>60</sup>     | To identify and modulate emotion processing in schizophrenia                                      | Abnormal brain activity to emotion identification induced by GABAergic modulation in first-degree relatives              | 11            |

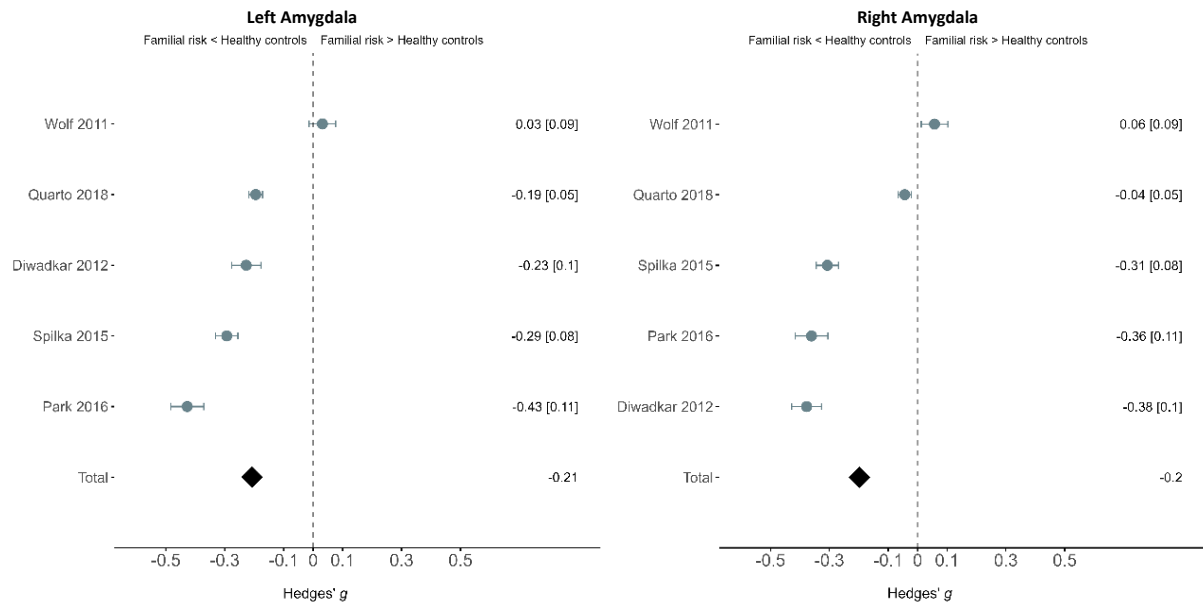
**Table S3. MNI coordinates of within-group meta-analysis.** We employed the Hammersmith brain atlas (n30r83, © Copyright Imperial College of Science, Technology and Medicine 2007. All rights reserved<sup>61</sup>) in order to determine the name of brain structures.

| 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  |

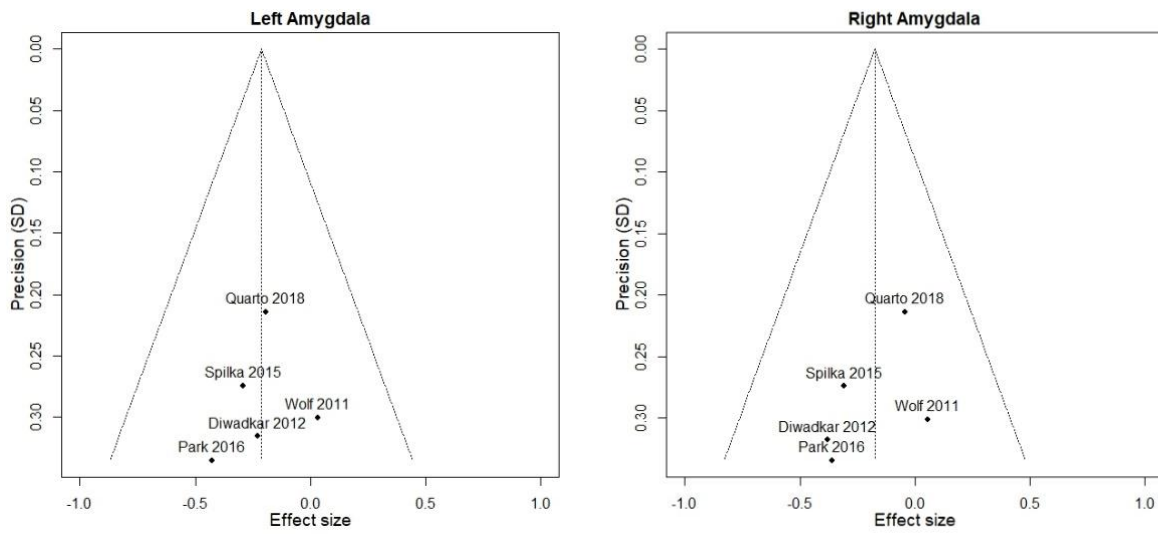
| Brain region | Hemisphere | MNI (x,y,z) | SDM-Z |
|--------------|------------|-------------|-------|
|--------------|------------|-------------|-------|

**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 reserved<sup>61</sup>) in order to determine the name of brain structures.

| Brain region  | Hemisphere | MNI (x,y,z)   | SDM-Z    |
|---|------------|---------------|----------|
| <i>First-degree relatives &lt; 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 |

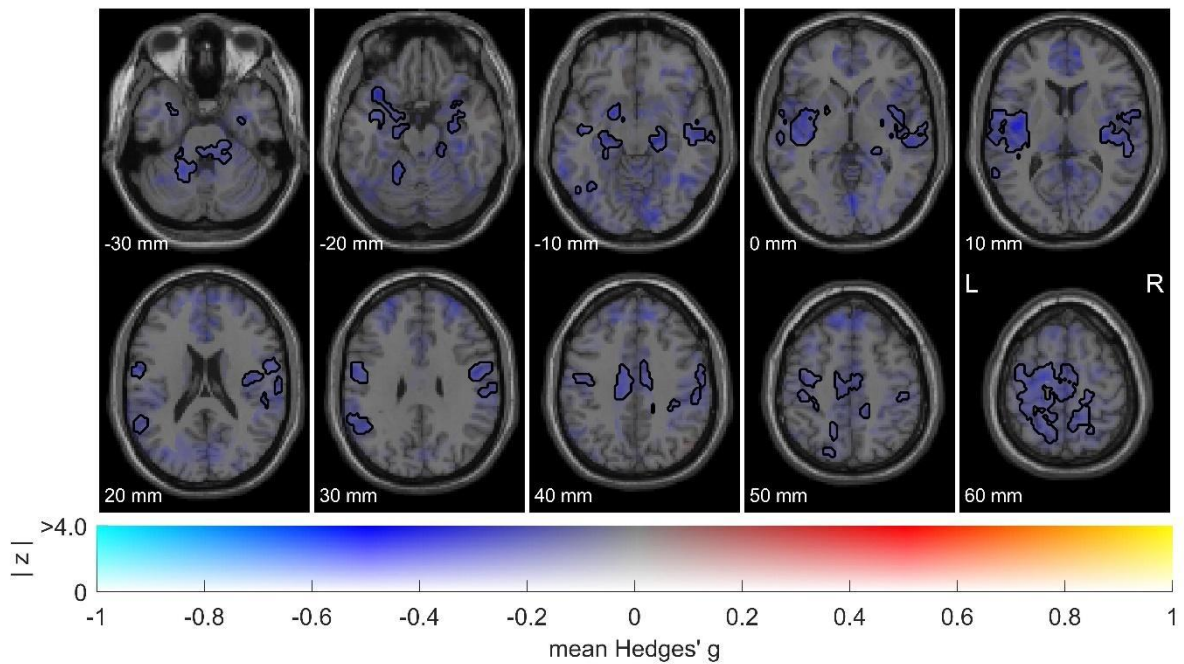


**Supplementary Figure S1. Forest plots** depicting the mean  $\pm$  variance of effect sizes for group comparison in the left and right amygdala (defined using the Melbourne Subcortex Atlas<sup>62</sup>). The black diamonds represent the overall effect size.



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

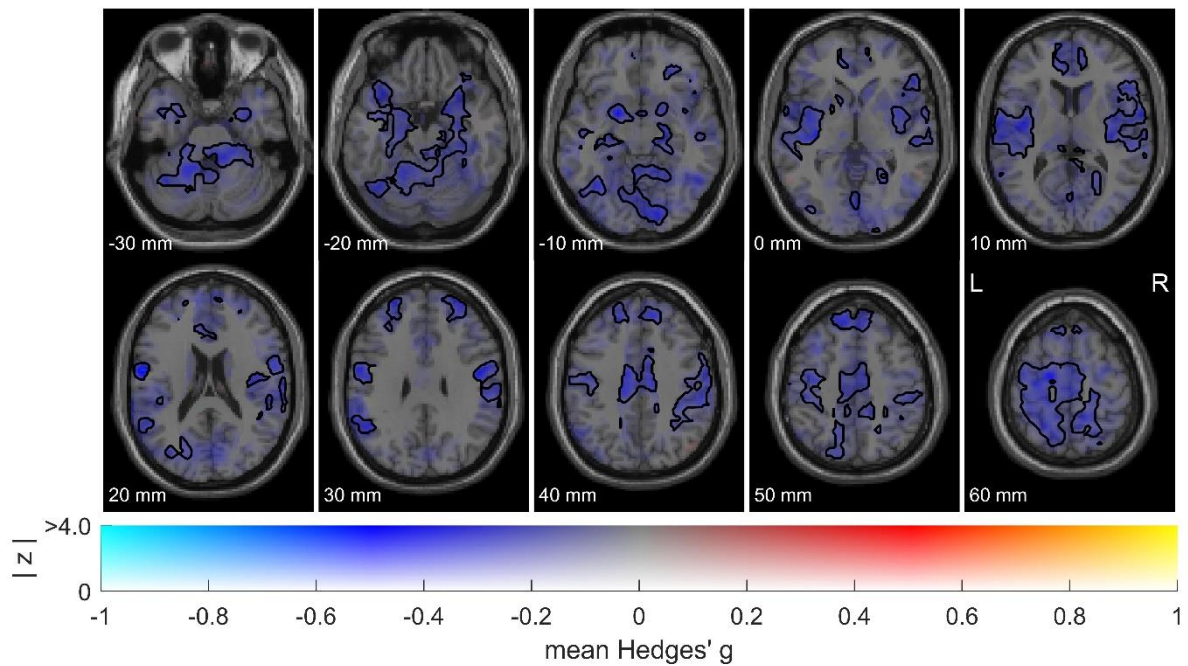
### First-degree relatives > Healthy controls



**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<sup>63,64</sup> 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  $p_{TFCE} < 0.05$ .*

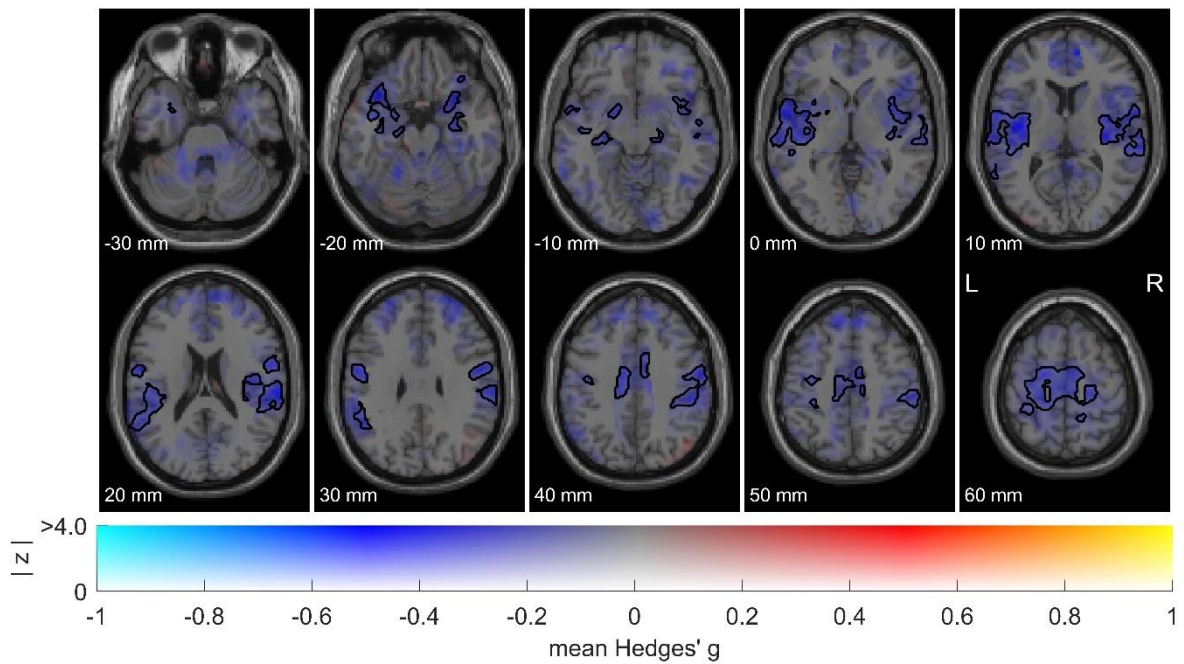


### First-degree relatives > Healthy controls



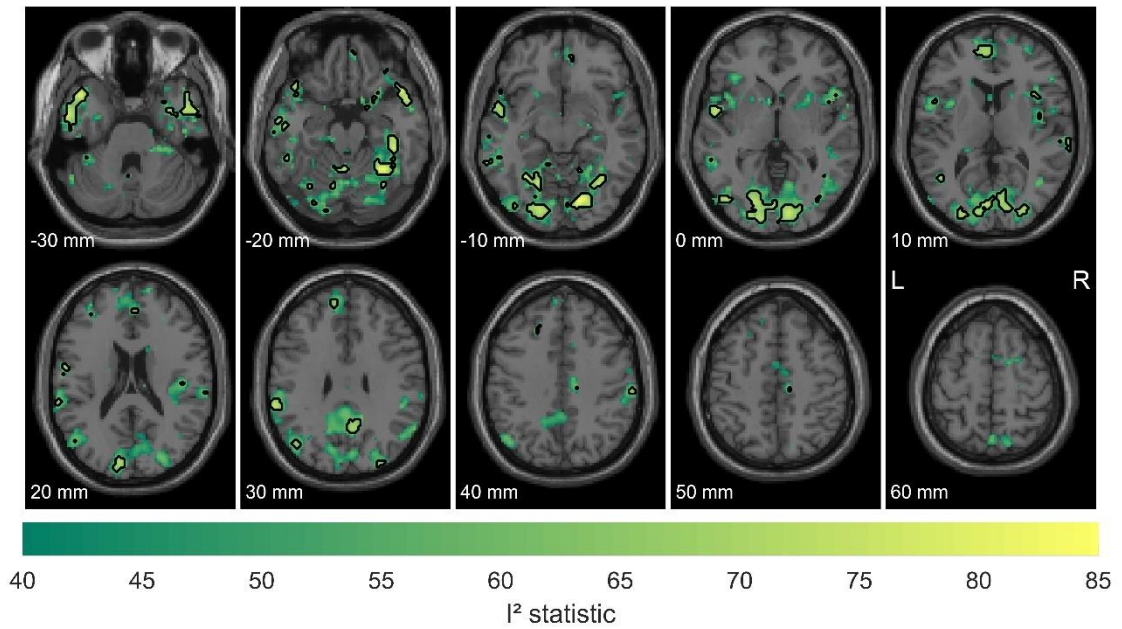
**Supplementary Figure S4. Meta-analysis without studies with partial brain coverage** (1 study excluded<sup>60</sup>,  $n = 4$  studies; 100 first-degree relatives and 125 healthy controls). *These are dual-coded images<sup>63,64</sup> in which color represents mean Hedges' g (brain regions showing 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<sup>63,64</sup> 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 heterogeneity<sup>65</sup>, 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**

Fiorito *et al.*

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References

## 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

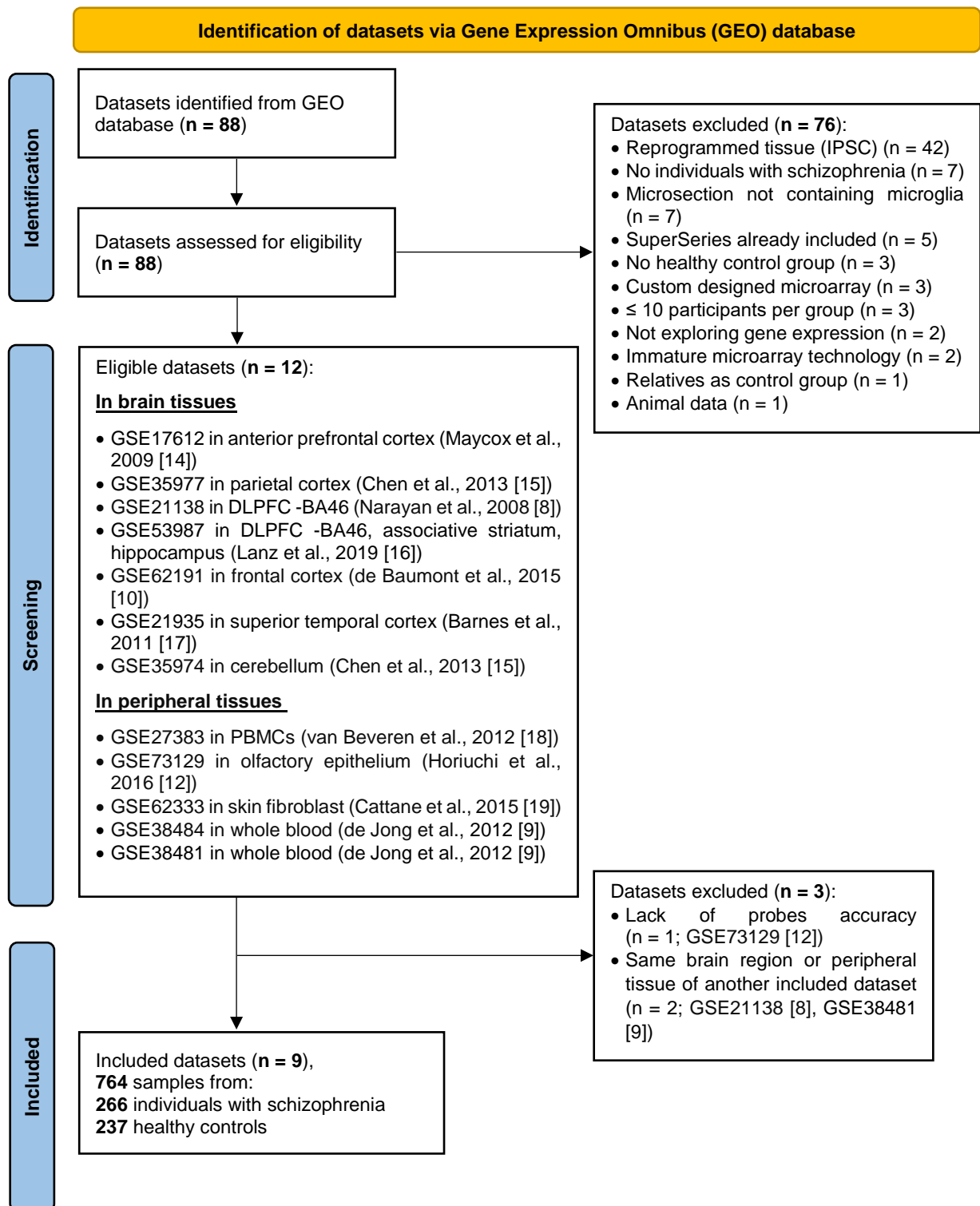
list of candidate genes. However, this criterion precluded the inclusion of other array platforms capable of exploring these candidate genes (such as Agilent or Illumina arrays). Therefore, this criterion was removed, and only custom-designed microarrays were excluded. Consequently, an additional non 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   | Yes        | 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          | 6.47 | 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          | 6.88 | 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  | 7.27         | 7.54 | 4.71       | 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 | 1.11       | 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        |      | NA         |      | 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 | 7.07       | 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   | 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(TM6EM119) |      |
|------------------|------------|------|------------|------|-------------|------|--------------|-------|------------|------|-------------|------|------------|------|------------|------|------------|------|----------------|------|
|                  | 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(TM6EM119) |      |
|------------------|------------|------|------------|------|-------------|------|--------------|------|------------|------|-------------|------|------------|------|------------|------|------------|------|----------------|------|
|                  | 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         | 29   | 29          | 29   | 30           | 29   | 30         | 28   | 30          | 28   | 30         | 29   | 30         | 29   | 30         | 29   | 30            | 29   | /    |
| Missing                   | 0    | 0          | 1    | 0           | 0    | 0            | 0    | 0          | 1    | 0           | 1    | /          | /    | 0          | 0    | 0          | 0    | 0             | 0    | /    |
| Mean                      | 3.10 | 3.11       | 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 | /             | /    | /    |
| SD                        | 0.35 | 0.24       | 0.34 | 0.37        | 0.30 | 0.51         | 0.39 | 0.33       | 0.20 | 0.30        | 0.25 | /          | /    | 0.32       | 0.22 | 0.47       | 0.37 | /             | /    | /    |
| Normality                 | Yes  | Yes        | Yes  | Yes         | No   | Yes          | No   | No         | Yes  | Yes         | No   | /          | /    | Yes        | Yes  | No         | Yes  | /             | /    | /    |
| Homoscedasticity          | No   | Yes        | Yes  | Yes         | Yes  | No           | No   | Yes        | Yes  | Yes         | Yes  | /          | /    | Yes        | Yes  | Yes        | Yes  | /             | /    | /    |
| Max                       | 3.84 | 3.58       | 2.60 | 4.19        | 4.08 | 3.77         | 3.58 | 1.98       | 1.51 | 1.82        | 1.49 | /          | /    | 2.69       | 2.01 | 3.05       | 2.68 | /             | /    | /    |
| Min                       | 2.55 | 2.40       | 1.16 | 2.68        | 2.55 | 1.87         | 1.66 | 0.82       | 0.84 | 0.76        | 0.74 | /          | /    | 1.21       | 1.09 | 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           | 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    |
| 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          | 7.00 | 6.98 |
| 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          | 0.15 | 0.14 |
| Normality                 | Yes  | Yes        | No   | Yes         | Yes  | Yes          | Yes  | Yes        | Yes  | Yes         | Yes  | Yes        | Yes  | Yes        | No   | Yes        | No   | Yes           | Yes  | No   |
| Homoscedasticity          | Yes  | No         | No   | Yes         | Yes  | Yes          | Yes  | No         | No   | Yes         | Yes  | Yes        | No   | No         | 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          | 7.38 | 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          | 6.71 | 6.55 |

**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><b>Sample collection:</b> University of Pittsburgh brain bank</p> <p><b>Consent / Ethics:</b> 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><b>SZ:</b> 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><b>Healthy controls:</b> 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><b>Original study:</b> Lanz <i>et al.</i>, Translational Psychiatry, 2019 (PMID: 31123247)</p> <p><b>Objective:</b> To evaluate shared transcriptional alterations across connected brain regions in SZ, bipolar disorder (BD), major depressive disorder (MDD) individuals, or HC</p> <p><b>Methods:</b> 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><b>Main results:</b> 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  |
|----------------------|--------|--------------------|---------------|----|----|--|
|                      |        |                    |               |    |    | <p><b>Sample collection:</b> Stanley Medical Research Institute's Neuropathology Consortium and Array Collections</p> <p><b>Consent / Ethics:</b> Specimens were collected with informed consent from next-of-kin</p> <p><b>SZ:</b> 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><b>HC:</b> 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><b>Exclusion criteria:</b> Individuals over age 65 were excluded</p> <p><b>Original study:</b> Chen <i>et al.</i>, Molecular Psychiatry, 2013 (PMID: 23147385)</p> <p><b>Objective:</b> 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><b>Methods:</b> 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><b>Main results:</b> 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> |
| GSE35977             | Brain  | Parietal cortex    | HuGene-1_0-st | 51 | 50 |  |
| 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><b>Sample collection:</b> Tissue collection of the Charing Cross Hospital, Imperial College London, UK</p> <p><b>Consent / Ethics:</b> 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 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><b>SZ:</b> 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><b>HC:</b> Mentally normal individuals from the community</p> <p><b>Exclusion criteria:</b> Alzheimer's disease, Parkinson's disease or multiple sclerosis were excluded</p> <p><b>Original studies:</b> Maycox <i>et al.</i>, Mol Psychiatry, 2009 (PMID: 19255580) Barnes <i>et al.</i>, J Neurosci Res, 2011 (PMID: 21538462)</p> |
| GSE17612             | Brain  | Anterior prefrontal cortex (BA10) | HG-U133_Plus_2 | 28 | 23 | <p><b>Objective:</b> To identify differentially expressed genes in anterior prefrontal cortex (BA 10) from SZ and HC</p> <p><b>Methods:</b> 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><b>Main results:</b> 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>   |
| GSE21935             | Brain  | Superior temporal cortex (BA22)   | HG-U133_Plus_2 | 23 | 19 | <p><b>Objective:</b> Gene ontology pathway enrichment analysis in BA22 and BA10 from SZ and HC</p> <p><b>Methods:</b> 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><b>Main results:</b> 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>  |

| 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><b>Sample collection:</b> Stanley Medical Research Institute's Neuropathology Consortium</p> <p><b>Consent / Ethics:</b> 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><b>SZ:</b> Records of all patients were reviewed for DSM-IV psychiatric diagnosis independently by two senior psychiatrists</p> <p><b>HC:</b> For normal controls, a structured telephone interview with a first-degree family member was carried out in all cases</p> <p><b>Exclusion criteria:</b> Participants with samples with low RNA integrity were excluded</p> <p><b>Original study:</b> De Baumont <i>et al.</i>, Schizophrenia Research, 2015 (PMID: 25487697)</p> <p><b>Objective:</b> To identify the molecular mechanisms that differentiate SZ and individuals with bipolar disorder from healthy controls</p> <p><b>Methods:</b> 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><b>Main results:</b> 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><b>Sample collection:</b> Erasmus University Medical Center (EMC), Rotterdam, The Netherlands</p> <p><b>Consent / Ethics:</b> 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><b>SZ:</b> 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 &lt;5 years) and age (&gt;15 and &lt;36 years)</p> <p><b>HC:</b> Age-matched controls were recruited from the students and staff of the EMC medical school and hospital</p> <p><b>Exclusion criteria:</b> 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><b>Original study:</b> van Beveren <i>et al.</i>, PLoS ONE, 2012 (PMID: 22393424)</p> <p><b>Objective:</b> 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><b>Methods:</b> Genome-wide expression study in the PBMCs of SZ and HC. Functional analysis of biological processes in which AKT1 gene is involved</p> <p><b>Main results:</b> 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  |
|                      |        |                    |                 |     |    | <b>Sample collection:</b> Department of Psychiatry, University Medical Center, Utrecht, The Netherlands / Parnassia PsychoMedical Center, The Netherlands / Center for Neuropsychiatric Schizophrenia Research, Psychiatric Center Glostrup, Denmark   |
|                      |        |                    |                 |     |    | <b>Consent / Ethics:</b> 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   |
|                      |        |                    |                 |     |    | <b>SZ:</b> 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)   |
|                      |        |                    |                 |     |    | <b>HC:</b> Unaffected controls   |
|                      |        |                    |                 |     |    | <b>Original study:</b> de Jong <i>et al.</i> , PLoS ONE, 2012 (PMID: 22761806)   |
|                      |        |                    |                 |     |    | <b>Objective:</b> To identify SZ-associated gene co-expression modules in the whole blood of SZ compared to HC   |
|                      |        |                    |                 |     |    | <b>Methods:</b> Genome-wide expression profiling from whole blood of 106 SZ and 96 HC. SZ-associated gene co-expression modules  |
|                      |        |                    |                 |     |    | <b>Main results:</b> 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><b>Sample collection:</b> Samples from Brescia and Verona, Italy</p> <p><b>Consent / Ethics:</b> 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><b>SZ:</b> 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><b>HC:</b> 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><b>Exclusion criteria:</b> For SZ and HC, exclusion criteria were defined as follows: mental retardation or cognitive disorder; serious somatic illnesses; uncorrected hypothyroidism or hyperthyroidism; age &lt;18 and &gt;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><b>Original study:</b> Cattane <i>et al.</i>, PLoS ONE, 2015 (PMID: 25658856)</p> <p><b>Objective:</b> Differential expression analysis in skin fibroblasts of SZ and HC</p> <p><b>Methods:</b> Genome-wide expression study comparing skin fibroblast transcriptomic profiles from 20 SZ and 20 HC</p> <p><b>Main results:</b> 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 <sup>1</sup> | Adjusted p-value <sup>2</sup> | Fold Change <sup>1</sup> | Adjusted p-value <sup>2</sup> | Fold Change <sup>1</sup> | Adjusted p-value <sup>2</sup> | Fold Change <sup>1</sup> | Adjusted p-value <sup>2</sup> |
| <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

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

<sup>2</sup>Significance 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 | Bayesian analyses<br>BF <sub>10</sub> | F-statistic          | p-value | Bayesian analyses<br>BF <sub>10</sub> | F-statistic | p-value | Bayesian analyses<br>BF <sub>10</sub> | F-statistic     | p-value | Bayesian analyses<br>BF <sub>10</sub> |
| <i>AIF1</i>   | 9.94        | 0.002   | 20.76                                 | 0.05                 | 0.37    | 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       | 5.99    | 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                                 | 0.08        | 12.37   | 0.08                                  | 16.89           | <0.001  | 531.55                                |
|               |             |         |                                       |                      |         |                                       |             |         |                                       |                 |         | 0.002                                 |

Abbreviations: BF<sub>10</sub>, Bayes Factor quantifying the evidence in favor of H<sub>1</sub> compared with H<sub>0</sub>; BF<sub>01</sub>, Bayes Factor quantifying the evidence in favor of H<sub>0</sub> compared with H<sub>1</sub>; 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 <sup>1</sup>      |       |
|               | Adjusted p-value <sup>2</sup> |       |
| <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 |

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

<sup>2</sup>Significance 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           |
| <i>AIF1</i>   | 10.01            | 0.002             |
| <i>CD68</i>   | 11.88            | <0.001            |
| <i>CSF1R</i>  | 22.48            | <0.001            |
| <i>CX3CR1</i> | 37.42            | <0.001            |
| <i>ITGAX</i>  | 3.41             | NS                |
| <i>IRF8</i>   | 6.86             | 0.009             |
| <i>OLR1</i>   | 15.19            | <0.001            |
| <i>TLR2</i>   | 16.43            | <0.001            |
|               |                  |                   |
|               | BF <sub>10</sub> | BF <sub>01</sub>  |
|               | 9.93             | 0.1               |
|               | 43.84            | 0.02              |
|               | 355.9            | 0.003             |
|               | 98837            | 0.00001           |
|               | 1.33             | 0.76              |
|               | 10.2             | 0.1               |
|               | 316.1            | 0.003             |
|               | 26.5             | 0.04              |

Abbreviations: BF<sub>10</sub>, Bayes Factor quantifying the evidence in favor of H<sub>1</sub> compared with H<sub>0</sub>; BF<sub>01</sub>, Bayes Factor quantifying the evidence in favor of H<sub>0</sub> compared with H<sub>1</sub>; NS, not significant

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