# Direction du regard & Comportement Prodromes comportementaux à l'apparition de symptômes psychotiques chez les enfants : exemple de la délétion 22q11.2

Marie-Noëlle Babinet

Université Lumière Lyon 2

École Doctorale Neurosciences et Cognition (NSCo ED 476)
Unité de Recherche Étude des Mécanismes Cognitifs (EMC EA 3082)
Institut des Sciences Cognitives Marc Jeannerod – Compréhension des mécanismes cérébraux, du comportement et des fonctions mentales (UMR 5229)

THESE

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# Direction du regard & Comportement

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Par Marie-Noëlle BABINET

Réalisée sous la direction du Professeur George A. MICHAEL et

de la Professeure Caroline DEMILY

**Devant le jury composé de :**

| | | |
|---|---|---|
| Frank LAROI | Professeur à l'Université de Liège (Belgique) | Président |
| Pauline CHASTE | Professeure à l'Université de Paris | Rapporteur |
| Nicolas BURRA | Maître de Conférence à l'Université de Genève (Suisse) | Rapporteur |
| Pierre FOURNERET | Professeur à l'Université Lyon 1 | Examinateur |
| Caroline DEMILY | Professeure à l'Université Lyon 1 | Directrice |
| George A. MICHAEL | Professeur à l'Université Lumière Lyon 2 | Directeur |

# RESUME

A l'ère où des liens de plus en plus étroits se créent entre neuropsychologie et psychiatrie, un focus sur la relation entre la perception du regard, la cognition sociale et les comportements prodromiques liés à l'émergence de symptômes psychotiques chez les enfants semble important. Les symptômes psychotiques, tels que les hallucinations et les idées délirantes, sont souvent précédés par des changements subtils dans le comportement, connus sous le nom de prodromes. La délétion 22q11.2 (22q11.2DS) est une anomalie génétique associée à un risque accru de développer des troubles psychotiques, ce qui en fait un modèle neurodéveloppemental. Les chercheurs ont constaté que les enfants porteurs de cette délétion présentent fréquemment des signes précurseurs de troubles psychotiques. Par ailleurs, des travaux de recherche ont montré que les enfants avec cette délétion ont tendance à présenter des schémas de direction du regard atypiques, tels qu'une préférence pour fixer des stimuli sociaux et non sociaux de manière différente par rapport aux enfants neurotypiques. Ces schémas peuvent inclure des périodes de regard prolongé sur des objets ou des personnes spécifiques, ainsi que des difficultés à détourner leur regard des stimuli pertinents.

Ces observations suggèrent que les anomalies dans la direction du regard associées à des comportements atypiques pourraient servir de marqueurs préliminaires chez les enfants à risque de développer des symptômes psychotiques tels que dans le 22q11.2DS. Nous avons ainsi mené plusieurs études expérimentales dans le but de répondre à certaines questions. L'ensemble de nos résultats suggèrent l'importance d'évaluer très précocement le comportement des enfants à l'aide de signaux tels que la méfiance, la désorganisation et les hallucinations. De plus, nous avons noté que le traitement inhabituel des regards est principalement lié aux émotions et aux processus attentionnels et exécutifs. En effet, les capacités inhibitrices se sont avérées cruciales pour détecter les émotions par le regard. En outre, nous avons étudié la perception émotionnelle plus générale, incluant le contexte social et la prosodie, pour comprendre l'impact des symptômes psychotiques sur ces aspects. Nos résultats ont révélé des difficultés globales dans la perception émotionnelle chez les enfants à haut risque de psychose (22q11.2DS), indépendamment de leurs symptômes actuels. Enfin, ce travail de thèse a également souligné l'importance de se concentrer, dans de futures études, sur les distorsions de reconnaissance (du regard et des émotions) plutôt que sur les déficits.

**Mots-clés** : Délétion 22q11.2, Détection du regard, Prodromes comportementaux, Symptômes psychotiques, Médecine personnalisée.

# ABSTRACT

In an era where increasingly, close links are being created between neuropsychology and psychiatry, a focus on the relationship between gaze perception, social cognition and prodromal behaviours linked to the emergence of psychotic symptoms in children seems important. Psychotic symptoms, such as hallucinations and delusions, are often preceded by subtle changes in behaviour known as prodromes. The 22q11.2 (22q11.2DS) deletion is a genetic abnormality associated with an increased risk of developing psychotic disorders, making it a neurodevelopmental model. Researchers have found that children with this deletion frequently show early warning signs of psychotic disorders. Additionally, research has shown that children with this deletion tend to exhibit atypical gaze direction patterns, such as a preference for gazing at social and non-social stimuli differently than neurotypical children. These patterns may include periods of prolonged staring at specific objects or people, as well as difficulty in looking away from relevant stimuli.

These observations suggest that abnormalities in gaze direction associated with atypical behaviours could serve as preliminary markers in children at risk of developing psychotic symptoms such as in 22q11.2DS. We have therefore conducted several experimental studies in order to answer certain questions. All of our results suggest the importance of assessing children's behaviour very early using signals such as distrust, disorganization and hallucinations. Additionally, we noted that unusual gaze processing is primarily related to emotions and attentional and executive processes. Indeed, inhibitory abilities have proven to be crucial in detecting emotions through gaze. In addition, we investigated broader emotional perception, including social context and prosody, to understand the impact of psychotic symptoms on these aspects. Our results revealed global difficulties in emotional perception in children at high risk for psychosis (22q11.2DS), regardless of their current symptoms. Finally, this thesis work also underlined the importance of focusing, in future studies, on recognition distortions (of gaze and emotions) rather than on deficits.

**Keywords:** 22q11.2 deletion syndrome, Gaze detection, Behavioural prodromes, Psychotic symptoms, Personalized medicine.

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# INTRODUCTION GENERALE

# I. Les maladies rares au service d'une meilleure compréhension des liens entre neurodéveloppement et psychiatrie

*"Awareness of these diseases. That is the key for patients being diagnosed. Even though we've made some huge strides - there are still too many stories of people struggling to get diagnosed. And quite often we're told 'it' in your head"* (Rarediseaseday.org)

## A - Qu'est-ce qu'une maladie rare ?

Le concept de maladie rare repose sur la définition épidémiologique statistique de prévalence donnée par l'Organisation Mondiale de la Santé (OMS) en 1967. Selon le critère de l'Organisation Mondiale de la Santé (OMS), une maladie est dite rare lorsqu'elle touche moins d'une personne / 2000 dans la population générale.
En France, pour une population totale de l'ordre de 68 millions d'habitants (*données Insee parue le 17-01-2023)*, cette définition s'applique à toutes maladies dont le nombre de personnes vivantes contemporaines ne dépasse pas 30 000.
Plus de 7000 maladies rares sont identifiées dont plus de 80% sont d'origine génétique (Nguengang Wakap et al., 2020). Individuellement chaque maladie rare représente peu de personnes et de ce fait sont très méconnues et n'ont bénéficié que de peu d'intérêt pendant de nombreuses années. Cependant, collectivement, 8 à 10% de la population mondiale est touchée par ces maladies rares, soit en France environ 4 à 5 millions de personnes (soit globalement une proportion similaire à celle de personnes atteintes de diabète) (Nguengang Wakap et al., 2020). On assimile souvent le terme de maladie rare à celui de maladie orpheline**.** Ce terme fait référence au manque d'intérêt qu'elles ont longtemps suscité, à l'absence de traitement ou à l'insuffisance des connaissances vis-à-vis de leur étiologie. Cependant, même si malheureusement la plupart des maladies rares sont orphelines, toutes les maladies orphelines ne sont pas rares ainsi que l'illustre l'exemple de la trisomie 21 qui a une incidence mondiale de 1 pour 800 naissances (Bull, 2020). Actuellement d'importants travaux de recherche sont consacrés aux maladies rares et l'industrie pharmaceutique s'intéresse également de près au

développement de thérapies innovantes les concernant comme les thérapies du gène, les thérapies géniques ciblées, les thérapies cellulaires ou le développement de molécules ciblant de près les causes identifiées (Nguengang Wakap et al., 2020). Il ne faut donc pas considérer ces termes comme synonymes, l'avancée des connaissances a progressé très vite ces dernières années dans le thème des maladies rares et on peut donc sérieusement penser que très prochainement elles ne seront plus orphelines.

## B - Une maladie rare : un modèle biologique, neurologique et génétique pour le neurodéveloppement

Les maladies rares, bien qu'elles puissent être relativement rares dans la population générale, sont souvent étudiées en tant que modèles biologiques, neurologiques et génétiques pour le neurodéveloppement en raison de certaines caractéristiques uniques qu'elles présentent. Il convient de citer plusieurs raisons pour lesquelles les maladies rares peuvent être utilisées comme modèle. Tout d'abord, les maladies rares sont souvent causées par des mutations génétiques spécifiques et bien définies (environ 80% sont d'origine génétique (Nguengang Wakap et al., 2020; Rath & Bailly, 2019)). Elles offrent donc une opportunité d'étudier les effets de ces mutations sur le développement tant sur le plan neurologique que cognitif. En identifiant les gènes impliqués dans ces maladies rares, les chercheurs peuvent mieux comprendre les voies biologiques et les mécanismes moléculaires sous-jacents au développement typique du cerveau. Dans la lignée de cette première raison, il est assez facile de comprendre les effets spécifiques que peuvent avoir les maladies rares sur le développement du cerveau et du système nerveux. Etant associées à des symptômes neurodéveloppementaux, tels que des retards de développement, des troubles cognitifs ou des troubles du spectre autistique, l'étude des maladies rares permet de fournir des informations précieuses sur les mécanismes sous-jacents du neurodéveloppement, y compris la plasticité cérébrale, la formation des circuits et l'apprentissage (Richter et al., 2015). En s'intéressant à ces altérations potentielles, les chercheurs peuvent également mieux appréhender les processus normaux du développement cérébral. Enfin, grâce à une compréhension fine du phénotype, le développement de prises en charge personnalisées ou de thérapies ciblées peut être envisagé. En somme, en étudiant ces maladies rares, les chercheurs peuvent mieux comprendre les

mécanismes sous-jacents du développement du cerveau et comment les anomalies génétiques peuvent affecter ce processus (Richter et al., 2015). Cette compréhension peut ensuite être appliquée à d'autres troubles du développement du cerveau, tels que l'autisme et la schizophrénie, qui peuvent avoir des causes génétiques similaires.

Il convient de noter que prendre les maladies rares comme modèle présente également des défis. Les échantillons de patients peuvent être limités, rendant les études plus difficiles à réaliser (Nguengang Wakap et al., 2020). De plus, les résultats obtenus à partir de maladies rares doivent être interprétés avec prudence, car ils ne peuvent pas être directement généralisables à d'autres conditions plus courantes (Richter et al., 2015).

## C - La neuropsychologie au service des maladies rares

Indiscutablement, la neuropsychologie se positionne en tant qu'élément central dans la quête d'une meilleure appréhension des maladies rares, en permettant une évaluation minutieuse des facettes cognitives, adaptatives et comportementales chez les individus qui en sont affectés. Cette discipline revêt une importance capitale en offrant les moyens d'identifier et de caractériser les profils cognitifs spécifiques, avec leurs compétences distinctives et leurs vulnérabilités inhérentes, associées, entre autres, aux maladies rares (Stirn, 2018). Plus spécifiquement, la contribution de la neuropsychologie s'élève à plusieurs niveaux. Tout d'abord, elle peut arborer un rôle crucial dans la détection précoce de troubles cognitifs et de déficits développementaux chez des individus porteurs d'une maladie rare. En identifiant minutieusement les schémas cognitifs, cette discipline a le potentiel de proposer un éclairage précoce sur les altérations fonctionnelles émergentes, offrant ainsi une opportunité précieuse pour une intervention précoce et ciblée. Plus encore, en s'engageant dans l'analyse de ces profils cognitifs, la neuropsychologie peut mettre en lumière les mécanismes neurobiologiques sous-jacents à ces perturbations. Cette perspective permet un enrichissement de la compréhension globale des mécanismes qui guident le développement et l'expression clinique des maladies rares. Un autre aspect important de la contribution de la neuropsychologie réside dans sa capacité à fournir une guidance pour le développement d'outils et d'échelles d'évaluation adaptés à chaque individu concerné par une maladie rare. En appréhendant les

nuances spécifiques des profils cognitifs, cette discipline peut contribuer à la création d'outils de mesure hautement personnalisés, qui reflètent, autant que faire se peut, les réalités cognitives de chaque patient. De plus, cette finesse dans l'évaluation peut alimenter la création de programme d'intervention et de prise en charge sur mesure, adressant directement les besoins spécifiques de chaque personne concernée. En résumé, la neuropsychologie joue un rôle de premier ordre dans l'exploration et la compréhension des maladies rares. Par son approche méthodique et éclairée, elle ouvre des fenêtres sur les dimensions cognitives et comportementales de ces conditions médicales rares, fournissant des repères essentiels pour la recherche et la pratique clinique. De l'évaluation initiale des profils cognitifs à la compréhension des mécanismes sous-jacents, en passant par la création d'outils et d'interventions adaptés, la neuropsychologie se dresse comme une alliée précieuse pour améliorer la qualité de vie des individus touchés par les maladies rares (Stirn, 2018).

# II. La délétion 22q11.2 : un modèle neurodéveloppemental de la schizophrénie à début très précoce

## A - Aspects génétiques, prévalence et diagnostic

Le syndrome de délétion 22q11.2 (22q11.2DS), aussi appelée syndrome vélo-cardio-facial ou syndrome de DiGeorge a été décrit dans les années 60' par le Dr Angelo DiGeorge. Il se manifeste par une micro délétion, généralement *de novo* (i.e., non héritée d'un ou des parents), d'environ 3Mb sur le bras long (q) du chromosome 22 en position 11.2. Lorsqu'un des deux parents est porteur, le risque de transmission de la délétion au fœtus est de 50% (Zinkstok et al., 2019). Les formes familiales ont un risque plus important d'engendrer des manifestations cliniques de plus grande sévérité (Schneider & Eliez, 2010). Le 22q11.2DS est fréquent et constitue le syndrome de microdélétion chromosomique le plus fréquent. La prévalence de ce trouble du neurodéveloppement a été estimée entre 1 pour 2000 et 1 pour 4000 naissances, sur la base du diagnostic de nourrissons atteints de malformations congénitales

majeures et de quelques études de dépistage de la population menées entre le début des années 1990 et le début des années 2000 à l'aide de la technologie d'Hybridation Fluorescente In Situ (FISH) (McDonald-McGinn et al., 2015; Novo et al., 2019). De par sa prévalence, le 22q11.2DS est une maladie rare (Santé & Candau, 1967). Dans la population générale, le 22q11.2DS est l'une des causes détectables les plus courantes de plusieurs affections : cardiopathie congénitale, immunodéficience, hypoparathyroïdie. Lorsque l'affection anténatale ou néo-natale est repérée, le diagnostic est précoce. Toutefois, il arrive que le diagnostic ne soit posé qu'ultérieurement, suite à des problèmes médicaux, ou bien à l'âge adulte si les aspects somatiques ne sont pas prépondérants et ne permettent pas de suspecter la pathologie dès le plus jeune âge. De plus, l'expression phénotypique de la pathologie est très variable d'un individu à l'autre, notamment en ce qui concerne la sévérité des troubles somatiques rencontrés. Certains individus peuvent présenter des problèmes cardiaques très sévères dès la naissance, alors que d'autres présentent des manifestations physiques relativement discrètes et aspécifiques (McDonald-McGinn et al., 2015). De ce fait, le taux de diagnostic de cette pathologie neurogénétique reste relativement bas (Schneider & Eliez, 2010).

## B - Manifestations cliniques et médicales

Les manifestations cliniques sont très variées et hétérogènes d'une personne à l'autre. Dans la petite enfance ou l'enfance, les symptômes typiques comprennent une combinaison de malformations cardiaques congénitales, d'infection chronique, de régurgitation nasale, de discours hypernasal, d'hypocalcémie, de difficultés d'alimentation et de retards de développement (Bassett et al., 2011; McDonald-McGinn et al., 2015; Novo et al., 2019). A l'adolescence et à l'âge adulte, des anomalies du comportement, dans de nombreux cas prodromiques d'une maladie psychiatrique (émergente), peuvent conduire au diagnostic lorsqu'elles sont associées à des manifestations cliniques sus-citées (Swillen & McDonald-McGinn, 2015). La présence d'un morphotype caractéristique, bien que subtil, peut faciliter le diagnostic à tout âge puisqu'il est présent chez 90% des patients. On retrouve notamment un faciès allongé, une rétrognathie, un nez proéminent, des yeux en forme d'amande, de petites oreilles, un aplatissement des pommettes, une fente palatine, des anomalies du voile du palais et un amincissement des doigts. Lorsque les manifestations cliniques sont frustres, certains

adultes ne sont diagnostiqués qu'après la naissance d'un enfant atteint (McDonald-McGinn et al., 2001).

## C - Les manifestations cognitives

Comme les manifestations médicales, le profil cognitif constitue un aspect tout aussi variable et hétérogène mais non négligeable du syndrome. Dans la petite enfance puis l'enfance et l'adolescence, les symptômes typiques comprennent une combinaison de retards de langage et de troubles des apprentissages (Bassett et al., 2011; Swillen & McDonald-McGinn, 2015). Les difficultés de motricité globale et fine (Swillen et al., 2005), ainsi que les retards de langage expressif et les problèmes d'élocution dominent chez les enfants préscolaires (Solot et al., 2000). Cependant, les déficits de la parole doivent être distingués des troubles du langage car les premiers s'améliorent généralement après une chirurgie correctrice vélo-pharyngée, alors que les troubles du langage peuvent survenir indépendamment de cette atteinte de la sphère oto-rhino-laryngologique et perdurer (Solot et al., 2000). Le niveau intellectuel des enfants et des adolescents suit une distribution normale comparable à celle de la population générale (De Smedt et al., 2007; Swillen et al., 1997). Toutefois, si un Quotient Intellectuel Total est calculable et calculé, il sera plutôt aux alentours de 70. Une dichotomie est également régulièrement observée entre l'Indice de Compréhension Verbale et l'Indice de Raisonnement Fluide en faveur du second en raison notamment des troubles du langage associés (De Smedt et al., 2007). Les difficultés d'apprentissage sont fréquentes au préscolaire et au primaire, notamment dans les domaines de mathématiques (De Smedt et al., 2009), et de la compréhension du langage (Glaser et al., 2002). Par ailleurs, les enfants seront possiblement mis en difficulté lorsque le matériel étudié fera appel aux capacités d'abstraction. Plusieurs études indiquent que le développement cognitif varie avec des trajectoires divergentes (Duijff et al., 2012; Fung et al., 2015) et que le niveau des capacités intellectuelles n'est pas nécessairement stable tout au long de la vie des personnes concernées. Bien que le Quotient Intellectuel Total soit généralement considéré comme un trait plus ou moins stable chez les jeunes au développement typique, une baisse moyenne de 7 points est observée chez des enfants, adolescents et jeunes adultes porteurs d'un 22q11.2DS (Vorstman et al., 2015).

D'autres domaines spécifiques de la cognition peuvent être impactés, tels que les

fonctions exécutives, les fonctions mnésiques, les fonctions visuospatiales et attentionnelles (Biswas & Furniss, 2016), ou encore la cognition sociale (Norkett et al., 2017). Les études rapportent une fréquence élevée (37% chez les enfants et 24% chez les adolescents) de Trouble du Déficit de l'Attention avec ou sans Hyperactivité (TDAH) dans le 22q11.2DS (Schneider et al., 2014). Plus précisément, il a été mis en évidence que les symptômes d'inattention étaient plus prononcés en comparaison à une population d'enfants sans la délétion (Antshel et al., 2007; Niarchou et al., 2015). Ces symptômes comprennent des difficultés à se concentrer et à maintenir l'attention, des difficultés à organiser des tâches, à oublier et à perdre facilement des choses (Loo et al., 2007; Niarchou et al., 2018). Les études qui visent à décrire précisément le fonctionnement des sous-systèmes attentionnels dans le 22q11.2DS mettent en évidence un système d'alerte efficient (Quintero et al., 2014; Stoddard et al., 2011) ainsi que des bonnes capacités à orienter le focus attentionnel vers des stimuli externes saillants (Shapiro et al., 2012; Stoddard et al., 2011). En revanche, des difficultés à orienter soi-même son attention vers des stimuli pertinents (Mannarelli et al., 2018; Shapiro et al., 2012), à traiter simultanément plusieurs informations (attention divisée) (Quintero et al., 2014; Stoddard et al., 2011) et un défaut d'inhibition associée à une impulsivité motrice et cognitive sont rapportées (Jonas et al., 2015; McCabe et al., 2014; Montojo et al., 2015). En d'autres termes, les composantes automatiques et/ou exogènes semblent efficientes alors que les composantes contrôlées et/ou endogènes sont plus susceptibles d'être altérées. En outre, peu d'informations sont disponibles sur certains systèmes attentionnels tels que l'attention soutenue de même que sur les trajectoires développementales. Il est par ailleurs assez clairement établi que les personnes ayant un 22q11.2DS présentent des compétences en cognition sociale plus faibles (Norkett et al., 2017), notamment dans les processus émotionnels et en théorie de l'esprit cognitive. Ces difficultés tant dans le traitement des émotions qu'en théorie de l'esprit, seraient liées en partie à des difficultés visuospatiales, à une stratégie atypique de traitement de l'information visuelle (Campbell et al., 2010; McCabe et al., 2011; Simon et al., 2005). Les autres domaines de la cognition sociale, tels que les biais attributionnels ou la perception sociale n'ont pas été étudiés (Norkett et al., 2017).

## D - Troubles comportementaux et psychopathologiques

De manière consensuelle, il est rapporté tant pour les enfants que les adultes avec un 22q11.2DS des compétences sociales plus faibles, y compris une labilité de l'humeur, une timidité et des difficultés à initier et maintenir des relations sociales, par rapport aux jeunes au développement typique (Campbell et al., 2015). Ces difficultés peuvent en partie être en lien avec l'émergence d'une psychose (Jalbrzikowski et al., 2012). Le 22q11.2DS est l'un des facteurs de risque génétique les plus robustes de la schizophrénie (1-2 % des cas) (Karayiorgou et al., 1995; Qin et al., 2020), et ce d'autant plus dans la schizophrénie à début précoce (jusqu'à 5.7%) (Addington & Rapoport, 2009). Réciproquement, environ 30 % des patients atteints du 22q11.2DS développent des symptômes psychotiques à l'adolescence ou au début de l'âge adulte (Monks et al., 2014). La fréquence de la schizophrénie est ainsi 25 fois plus élevée que dans la population générale (25 à 40% selon les études *versus* 1%) (Ivanov et al., 2003; Murphy et al., 1999; Shprintzen et al., 1992). Certaines études ont décrit en association au 22q11.2DS, une prédominance des signes négatifs de schizophrénie (difficulté à communiquer, difficulté à ressentir du plaisir, manque d'énergie et de motivation, pauvreté de la pensée, retrait social, diminution dans l'expression des émotions) avec une présentation plus déficitaire, mais ces résultats ne sont pas systématiquement retrouvés dans les études comparant les patients présentant une schizophrénie avec ou sans 22q11.2DS associé (Bassett et al., 2003). Par ailleurs, une dégradation des capacités intellectuelles, notamment dans le domaine du verbal, serait à l'adolescence, associée à un risque plus élevé de transition psychotique vers la schizophrénie (Vorstman et al., 2015). De plus, l'apparition précoce de symptômes psychotiques, tels que des illusions perceptives visuelles ou auditives, voire des hallucinations, parfois dès l'enfance sont également des facteurs prédictifs d'un risque d'évolution vers la schizophrénie (Antshel et al., 2010; Gothelf et al., 2007). Au-delà des liens bien établis entre signes psychotiques, schizophrénie et 22q11.2DS, il semble important de ne pas omettre d'autres comorbidités psychiatriques potentielles (Novo et al., 2019). En effet, les symptômes anxieux sont également fréquemment rapportés (35 % des enfants et 27 % des adultes) et ils peuvent s'exprimer sous différentes formes : phobiques (peur du noir, peur des animaux, peur des orages etc.), trouble anxieux généralisé, trouble obsessionnel, anxiété sociale (Philip & Bassett, 2011). L'anxiété peut se manifester à la fin de l'école primaire, à mesure que les apprentissages deviennent plus abstraits en raison des défis liés à ces apprentissages et à l'intégration sociale. Selon des propos rapportés par des familles et des enfants concernés, un vécu de moqueries voire de harcèlement peut être présent, constituant des facteurs de stress importants, facteurs associés à un risque plus élevé de transition psychotique vers la

schizophrénie (Chaumette et al., 2016). Enfin, il a été suggéré que la forte prévalence des comportements autistiques chez les enfants avec un 22q11.2DS ne devrait pas être considérée comme un Trouble du Spectre de l'Autisme, mais plutôt comme des symptômes prodromiques précédant l'apparition de la schizophrénie (Eliez, 2007; Karayiorgou et al., 2010; Van et al., 2017; Vorstman et al., 2006).

## III. Schizophrénie à début très précoce ou *Childhood Onset Schizophrenia* (COS)

C'est à partir du XX$^{ème}$ siècle que les troubles psychiatriques chez l'enfant et l'adolescent deviennent un sujet d'intérêt avec l'émergence de la pédopsychiatrie. En 1933, le psychiatre new-yorkais Howard Potter dans son livre *Schizophrenia in Children* (Potter, 1933) applique pour la première fois le terme de schizophrénie aux enfants. Depuis une soixantaine d'années, il est de plus en plus admis que certains enfants présentent un ensemble de difficultés sociales, de communication, de perception, de pensée, de comportements inhabituels et des préoccupations avec des idées atypiques qui ont un impact néfaste sur leur santé mentale et leur bien-être (Esterberg et al., 2010; Nagy & Szatmari, 1986; Roberts et al., 2001; Tantam, 1988). Il apparaît ainsi opportun de pouvoir repérer et/ou diagnostiquer cette psychopathologie neurodéveloppementale.

Il existe des approches historiques disparates de la reconnaissance de ces perturbations de type psychotique chez les enfants. Certains ne reconnaissent pas cette perturbation comme un trouble parce que « le caractère et la personnalité des enfants sont fluides et non persistants » (de Girolamo et al., 2022; van Os et al., 2009), ou tout au plus une manifestation d'états émotionnels réactifs de l'enfance, comme la dépression. D'autres ont conceptualisé le diagnostic de ces enfants dans les spectres de la schizophrénie ou de l'autisme dans les systèmes du Manuel Diagnostique et Statistique des troubles mentaux (DSM) et de la Classification Internationale des Maladies (CIM) par des termes tels que « Schizophrénie, type d'enfance » (DSM-I, DSM-II, CIM-8) (American Psychiatric Association, 1952, 1968; World Health Organization, 1968),

« Trouble Envahissant du Développement NOS (TED-NOS) » (DSM-III, DSM-IV-TR) (American Psychiatric Association, 1980, 2000), ou « autisme atypique » (CIM -10) (World Health Organization, 1992). Ces diagnostics sont restés mal définis et n'ont pas été retenus dans les éditions actuelles (DSM-5, ICD-11) (American Psychiatric Association, 2013; World Health Organization, 2019). Une autre approche pour catégoriser les enfants présentant des dysfonctionnements dans de multiples domaines émotionnels, comportementaux et sociaux, entre la schizophrénie et l'autisme (Ad-Dab'Bagh & Greenfield, 2001), était de les regrouper sous le terme de « syndrome borderline (psychotique) », un précurseur des catégories adultes distinctes des troubles de la personnalité borderline et schizotypique. Il apparaît que ces différentes tentatives de classification n'ont pas réellement permis d'obtenir une plus grande application diagnostique chez les enfants (Bemporad et al., 1982; Bentivegna et al., 1985; Greenman et al., 1986; Lofgren et al., 1991; Petti & Law, 1982).

Dans la littérature actuelle sur la schizophrénie précoce (Kendhari et al., 2016), la recherche longitudinale sur la psychopathologie chez les enfants, y compris la descendance à haut risque de parents/mères atteints de schizophrénie, a décrit des enfants ayant un comportement étrange, un rejet par les pairs, des troubles de la perception et de la pensée et un comportement antisocial. Ils étaient également plus susceptibles de développer une schizophrénie à l'adolescence ou au début de l'âge adulte. Une étude longitudinale historique du National Institut of Mental Health portant sur 160 enfants dont le dépistage des symptômes de la schizophrénie était positif a décrit un groupe d'enfants « présentant des troubles multidimensionnels » (McClellan & Werry, 1997; McKENNA et al., 1994). Ils présentaient des symptômes psychotiques transitoires, une réactivité émotionnelle, une préoccupation pour les fantasmes, des difficultés à interagir socialement et des déficits cognitifs tels qu'un traitement de l'information atypique ainsi que des compétences visuo-spatiales moindres (McClellan & Werry, 1997). La similitude de ces enfants avec les critères actuels du trouble de la schizophrénie est évidente. Ils appartiennent à un spectre de caractéristiques schizotypiques reconnaissables, influencées par des déterminants neurodéveloppementaux, génétiques et psychosociaux (Kendhari et al., 2016), qui varient de subtiles altérations du fonctionnement, à une perturbation clinique fluctuante mais persistante de symptômes psychotiques, et à son extrémité à la schizophrénie. Etant établi qu'un fonctionnement psychosocial atypique est présent chez les personnes présentant une schizophrénie ou étant à ultra haut risque de psychose (Kim et al., 2019), s'intéresser davantage aux soubassements de ces particularités semble primordial.

Les individus avec un fonctionnement psychosocial atypique peuvent avoir des difficultés à décoder correctement les indices sociaux, y compris ceux liés au regard et aux expressions faciales (Kossmann et al., 2021). Ils pourraient avoir du mal à reconnaître les émotions, les intentions ou les informations cachées véhiculées par le regard des autres. Cette difficulté pourrait être à l'origine des difficultés observées dans leur capacité à établir et à maintenir des relations sociales satisfaisantes. Ayant une influence sur le bien-être émotionnel et psychosocial de ces personnes, l'étude des mécanismes sous-jacents à ces difficultés, notamment en termes de traitement du regard et des émotions, semble ainsi être un axe prioritaire de recherche.

# IV. Traitement du regard et des émotions

*« Pourquoi tu me regardes comme ça ? »* (Léon[1], 7 ans)

La détection d'un regard, qu'il soit dirigé vers nous, qu'il regarde ailleurs ou qu'il exprime une émotion, est un signal social important puisqu'il renseigne directement sur l'intérêt de la personne, ce qu'elle souhaite et la présence d'éventuels dangers à proximité (Emery, 2000). Le visage humain est sans doute le stimulus visuel le plus important que nous traitons tous les jours car il nous informe sur la façon de nous comporter socialement : être capable de distinguer si la personne qui vient vers vous est votre ami, votre supérieur, votre ennemi et s'il a l'air en colère, triste ou heureux fera certainement une différence dans la façon dont vous interagirez avec lui.

La région des yeux du visage représente une zone particulière en raison de la grande quantité d'informations qui peuvent en être extraites (Burra et al., 2017). Plus que les autres traits du visage, les yeux sont au cœur de tous les aspects de communication sociale tels que les émotions et la direction de l'attention. Le domaine des neurosciences cognitives et comportementales s'est depuis quelques années intéressé à la complexité de ces processus. Le rôle central des

[1] Par soucis de confidentialité, le prénom a été modifié.

yeux et du regard dans la cognition sociale représente un point d'intérêt d'autant plus lorsque nous savons que des difficultés dans les interactions sociales en lien avec le regard et les émotions peuvent être retrouvés dans certains troubles psychiatriques, tels que la schizophrénie et par extension la schizophrénie à début précoce (Itier & Batty, 2009).

## A – Détecter le regard est complexe mais précoce

Le développement du regard chez le nourrisson est une partie essentielle de son développement perceptif et social. Les bébés naissent avec des capacités visuelles limitées, mais au fil des premiers mois de leur vie, leur vision s'améliore progressivement et ils commencent à explorer leur environnement visuel avec plus de précision (Bronson, 1974). Durant la période néonatale, alors que le nourrisson a une vision floue et limitée à une distance de 20 à 30 centimètres, les nouveau-nés vont progressivement être attirés par les contrastes visuels élevés, comme les visages humains, en particulier les yeux et la région du front (Bronson, 1974). Ce processus forme la base de la communication visuelle précoce (Itier & Batty, 2009). Outre le fait qu'il soit solidement établi que les nourrissons sont instinctivement attirés par les visages dès les premiers stades de la vie, les chercheurs se sont engagés dans une quête pour élucider les ramifications de l'attention et du comportement des nouveau-nés en ce qui concerne la détection et l'interprétation du regard qui leur est porté. Plus précisément, les investigations ont tenté de saisir l'impact des regards dirigés vers eux (regard direct) ou loin d'eux (regard détourné). Dans les premières investigations (Hood et al., 1998; Vecera & Johnson, 1995), des dissemblances de conduite étaient déjà observées chez les nouveau-nés, en fonction de ces deux contextes, avec une orientation préférentielle vers le regard direct. Cet attrait précoce pour les regards directs semble posséder un potentiel constructif pour le développement de diverses compétences relationnelles futures (Itier & Batty, 2009). De plus, il pourrait constituer un signe précoce aux premiers échanges sociaux, amorçant ainsi des réponses physiologiques autonomes (Hietanen, 2018). Les fondements de cette préférence envers les regards directs trouvent du soutien dans une variété de théories. Selon les propositions de Baron-Cohen (1994), il existerait un contexte visuel spécifique qui engendrerait des associations spatiales entre les différentes composantes faciales, facilitant ainsi la perception de la direction du regard. Une autre perspective (Batki et al., 2000; Langton et al.,

2000; Simion & Giorgio, 2015) avance que cette préférence pourrait résulter de biais attentionnels généraux envers les propriétés structurelles particulières des éléments présents dans un visage, notamment les yeux. En outre, les réflexions de Babinet et de ses collaborateurs (2022) laissent entrevoir la possibilité de leur intégration dans un cadre conceptuel plus vaste. A titre d'exemple, la détection et la perception des yeux pourraient impliquer une étape de codage visuel qui extrait les spécificités liées à l'éclairage, au grain et aux zones saillantes à contraste élevé du visage. Ce processus pourrait ainsi contribuer à la capture d'éléments tels que la pose statique et les expressions faciales observées (Bruce & Young, 1986). En résumé, cette exploration de la préférence pour les regards directs chez les nouveau-nés s'inscrit dans un paysage conceptuel riche et complexe, où les nuances perceptuelles se mêlent aux implications développementales et probablement sociétales.

Au-delà du fait que la perception d'un regard est une faculté qui semble primordiale à notre développement social, comprendre comment nous interprétons le regard d'autrui paraît tout aussi indispensable.

## B – Chercher à comprendre les interprétations du regard est primordial

Comprendre les interprétations du regard est essentiel pour décoder les émotions, les intentions et les signaux sociaux émis par les autres (Emery, 2000). Alors que le regard peut sembler une partie infime du corps humain, il est finalement un moyen puissant de communication non-verbale, et peut révéler beaucoup d'informations sur ce que les gens pensent et ressentent (Itier & Batty, 2009). En effet, à travers différentes modulations du regard, les informations véhiculées vont être multiples. Il est par exemple possible d'observer un contact visuel prolongé pouvant indiquer de l'intérêt, de la confiance ou de l'engagement, ou bien plutôt fuyant, signalant de la timidité, de l'anxiété ou du désintérêt pour la personne qui se trouve en face de nous. Les yeux sont également le siège des expressions faciales, permettant à l'aide d'autres caractéristiques (sourcils, bouche, front), de transmettre un message émotionnel. De plus, la direction vers laquelle quelqu'un regarde peut donner des indices sur ce qui attire son attention (Itier & Batty, 2009). Si quelqu'un regarde quelque chose de spécifique, il est probablement intéressé ou concentré sur cet objet ou cette personne. A contrario, si quelqu'un

détourne subitement le regard pendant une conversation, cela peut indiquer qu'il cache quelque chose, se sent gêné ou est mal à l'aise. Enfin, d'autres caractéristiques du regard peuvent être modulées et avoir un impact sur son interprétation telles que la dilatation des pupilles ou bien l'intensité du regard.

Etant donné l'importance que revêt la détection et l'interprétation du regard dans le contexte des interactions sociales, il est tout à fait raisonnable de prévoir que toute altération de la capacité à repérer ou à suivre le regard d'autrui puisse avoir des répercussions significatives sur la manière dont nous appréhendons la cognition et les comportements sociaux (Itier & Batty, 2009; Kleinke, 1986). En effet, cette perturbation potentielle peut se traduire par des nuances subtiles mais impactantes dans la dynamique interpersonnelle, ayant également un rôle dans les interactions humaines. Lorsque cette compétence fondamentale est compromise, elle peut entraîner des conséquences multiples. Les individus pourraient se retrouver dans l'incapacité de saisir pleinement les intentions et les émotions d'autrui, ce qui pourrait, en retour, engendrer des malentendus et des échecs de communication. En conséquence, les relations interpersonnelles pourraient se fragiliser, laissant place à des interprétations erronées, voire à une perte de confiance. De plus, les erreurs potentielles dans la perception du regard peuvent donner lieu à une distorsion dans la compréhension des états mentaux d'autrui, conduisant ainsi à des hypothèses incorrectes quant aux pensées et aux motivations des autres (Cañadas & Lupiáñez, 2012). Un point tout aussi important à noter est que ces difficultés de perception du regard pourraient également agir comme des marqueurs subtils de mal-être psychique sous-jacent. Les individus qui présentent des troubles de santé mentale pourraient être particulièrement vulnérables à ces altérations, ce qui soulève la question de savoir si les atypicités de perception du regard pourraient être utilisés comme des indicateurs préliminaires dans le domaine de la santé mentale (Emery, 2000). En somme, la complexité de cette interaction entre la perception du regard, la cognition sociale et le bien-être psychologique nécessite une attention approfondie, à la fois dans le cadre de la recherche scientifique mais également dans celui de la compréhension pratique de la manière dont nous interagissons les uns avec les autres.

*« Dès le petit déjeuner, ma sœur est méchante, je ne veux pas qu'elle me regarde »* (Léon, 7 ans).

La question de savoir comment un regard perçu comme menaçant peut engendrer des obstacles au sein des relations, voire refléter un mal-être psychique, suscite un intérêt considérable. Les mécanismes sous-jacents à ce phénomène complexe ont fait l'objet de nombreuses études approfondies. En effet, ces recherches se sont concentrées sur les connexions entre la manière dont le regard est perçu, la détection des émotions et mêmes des conditions telles que la schizophrénie (Abbott et al., 2018; Franck et al., 1998, 2002; Kohler et al., 2008; Tso et al., 2012). Analyser ces interactions entre la perception visuelle, la cognition émotionnelle et les états psychologiques permet de jeter une lumière nouvelle sur les défis que peut représenter l'interprétation des regards dans le contexte des interactions sociales et de la santé mentale.

## V. Objectifs et articulation du manuscrit

Depuis de nombreuses années, les chercheurs tentent de comprendre les soubassements de la schizophrénie, les troubles cognitifs associés et les réseaux neuronaux sous-jacents à l'origine des déficits expliquant cette psychopathologie. La schizophrénie est une pathologie mentale se manifestant par des idées délirantes, des hallucinations et des troubles cognitifs (Tandon et al., 2013). Il s'agit d'un enjeu de santé publique du fait de son important retentissement sur les personnes concernées mais également leurs proches. La prise en charge de ces personnes requière des actions de prévention et une articulation des soins dans le but d'une réinsertion précoce (Franck, 2021). En ce sens, les recherches sur les signes précurseurs d'apparition de symptômes psychotiques voire de schizophrénie, devraient s'inscrire aujourd'hui dans la dynamique de la neuropsychologie expérimentale (Oscar-berman, 1989). Il s'agit de (i) comprendre via l'étude des altérations spécifiques du fonctionnement cérébral, qui peuvent survenir suite à un trouble du neurodéveloppement, une maladie rare, l'organisation et le fonctionnement des processus mentaux normaux (c'est l'objectif visé par la psychologie cognitive (Rumelhart, 1977)) ; et (ii) d'identifier les substrats cérébraux du comportement et de la cognition (cela s'inscrit aujourd'hui dans les neurosciences cognitives (Krendl & Betzel, 2022)).

Les objectifs de ce travail de thèse sont multiples : (i) mieux dépister ces jeunes à haut risque de psychose pour mieux les accompagner, et (ii) contribuer à la littérature sur la perception et la détection du regard et des émotions pour mieux appréhender les dysfonctionnements potentiels liés à la schizophrénie très précoce. Dans les chapitres qui vont suivre, nous présenterons les études expérimentales menées au cours de cette thèse ainsi qu'une revue systématique de littérature ayant permis d'ouvrir le champ de nouvelles études expérimentales. Dans l'Étude 1, nous présenterons le développement ainsi que l'étude psychométrique d'une nouvelle échelle de dépistage des symptômes psychotiques précoces chez l'enfant de 4 à 13 ans. Par la suite, avant de présenter diverses études expérimentales sur le regard, une revue systématique de littérature sur ce sujet permettra de poser les bases théoriques qui ont servi à l'élaboration des études. L'Étude 2 tentera de faire la lumière sur le déroulement temporel de la perception du regard, point d'ombre soulevée dans la revue de littérature précédente. L'Étude 3 consistera en une première investigation des capacités à détecter le regard chez des enfants à haut risque de psychose (en prenant la délétion 22q11.2 comme modèle). L'Étude 4 présentera comment les enfants porteurs d'une délétion 22q11.2 perçoivent les émotions faciales, que ce soit sur un visage, en contexte ou via la voix. Enfin, l'Étude 5 examinera le rôle de la présence de symptômes psychotiques précoces sur la perception émotionnelle. Dans la dernière partie, nous ferons la synthèse des différents résultats récoltés au cours de ce travail de thèse en revenant sur quelques questions fondamentales : la perception du regard est-il un indicateur précoce d'apparition de symptômes psychotiques ? Quels facteurs influencent notre capacité à percevoir le regard et les émotions ? Quelles sont les nouvelles pistes de recherches sur la détection du regard émotionnelle ou neutre ?

# CHAPITRE 1

## Le dépistage des symptômes psychotiques précoces de l'enfant

# La nécessité d'une nouvelle échelle de dépistage

La schizophrénie peut être considéré comme un trouble neurodéveloppemental d'étiologie multifactorielle (McCutcheon et al., 2020). La schizophrénie pédiatrique comprend la schizophrénie précoce – « Early-Onset schizophrenia » - (début avant l'âge de 18 ans) et la schizophrénie très précoce – « Childhood Onset Schizophrenia » - (début avant l'âge de 13 ans) (Kendhari et al., 2016). L'adolescence a été établie comme une période critique pour l'élagage neuronal (Germann et al., 2021). Avec l'apparition précoce des symptômes, il peut ainsi y avoir une perturbation du processus typique de développement neuronal, entraînant des troubles de la mémoire, de la pensée abstraite et de la régulation des émotions. Bien que la prévalence de la schizophrénie soit de 1 % dans la population générale, l'incidence de la schizophrénie pédiatrique est rare (Driver et al., 2013; McClellan & Werry, 1997; McKENNA et al., 1994). L'évaluation de l'apparition de symptômes psychotiques chez l'enfant n'est pas aisée en raison des nombreux diagnostics différentiels qui peuvent rentrer en compétition (Kendhari et al., 2016). Par conséquent, il est important d'évaluer finement la cause de tout symptôme psychotique d'un enfant ou d'un adolescent, en s'aidant de l'histoire neurodéveloppementale mais également des intrications génétique-environnement. Peu d'outils d'aide au dépistage existent, même si un diagnostic précis et précoce est important pour traiter les enfants le plus tôt possible et améliorer leur qualité de vie future (McClellan, 2018). La mise en place d'un traitement antipsychotique associée à une psychothérapie et une psychoéducation, est d'ailleurs un facteur de meilleur pronostic futur (Kane et al., 2016).

Ainsi, cette première étude a pour objectif d'élaborer et de valider un nouvel outil de dépistage des symptômes psychotiques précoces chez l'enfant. Pour cela, nous avons développé une nouvelle échelle, rapide à administrer et qui est rempli par les parents de l'enfant. Elle se décline sous deux versions : une permettant l'évaluation du comportement actuel de l'enfant et l'autre, évaluant le comportement de l'enfant lorsqu'il avait deux ans. S'intéresser aux comportements à deux ans permet d'estimer la présence ou non des symptômes dès cet âge-là. D'un point de vue plus fondamentale, l'échelle permet d'étudier l'évolution des symptômes de l'enfant. L'objectif de cette étude a donc été double : (i) développer un outil de dépistage des symptômes psychotiques précoces de l'enfant, (ii) rechercher la présence de ces symptômes à l'âge de 2 ans et dans le présent. A cet effet, une validation psychométrique de l'échelle a été, dans un premier temps, menée. Dans les suites, une comparaison inter-groupes a été réalisée

afin d'étudier les profils développementaux de trois groupes d'enfants : neurotypiques, porteurs d'un trouble du neurodéveloppement sans symptômes psychotiques et porteurs d'un trouble du neurodéveloppement avec symptômes psychotiques. L'originalité de cette étude repose, entre autres, sur cet aspect de profil développemental distinct.

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# A new scale for the screening of childhood early psychotic symptoms

Marie-Noëlle Babinet [a,b,*], Caroline Demily [a], George A. Michael [b]

[a] Centre de Rérence Maladies Rares Troubles du Comportement d'Origine Génétique (GénoPsy Lyon), Centre d'excellence Autisme iMIND, Centre Hospitalier Le Vinatier, UMR 5229, CNRS & Université Lyon 1, 95 Boulevard Pinel, Bron 69500, France

[b] Unité de Recherche Étude des Mécanismes Cognitifs, Université Lumière Lyon 2, Université de Lyon, 5 avenue Pierre Mendes-France, Bron 69676 CEDEX, France

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ABSTRACT

This study aimed to develop a new scale, the Early Psychotic Symptoms screening scale (EPSy), to assess the prodromes of psychotic symptoms in children aged 4 to 13 years. Two versions were proposed: one to assess the child's current behavior and one to assess the child's behavior when he/she was 2 years old. The second aim of this study was to investigate the presence of these symptoms at the age of 2 years and their evolution up to the child's current age. The analysis of EPSy identified three main factors, namely mistrust/paranoia, perceptual aberrations/hallucinations and disorganized symptoms. It has good psychometric properties. Data also shows that, independently of the participant's age, the total score on the 2-years-old version predicts the total score on the current-age version, and this is also the case for each individual factor. Finally, it is of clinical interest since it makes it possible to describe symptomatology both at age 2 and at the child's present age depending on the group to which the children are assigned (control children, psychotic children, non-psychotic children).

## 1. Introduction

### 1.1. Clinical presentation of schizophrenia spectrum disorders in childhood

Recent interest in the neurodevelopmental trajectories of schizophrenia spectrum disorders (SSDs) has led to an increased focus on the early developmental period (Gogtay et al., 2011; Kendhari et al., 2016). Pediatric schizophrenia describes schizophrenia experienced by patients with an initial presentation before adulthood and is currently diagnosed with *DSM-5* diagnostic criteria similar to those used for adult schizophrenia. Childhood-Onset Schizophrenia (COS) is defined as schizophrenia with symptom onset between the ages of 5 (Russell, 1994) and 13 years (Kendhari et al., 2016). As in the case of adult schizophrenia, psychotic symptoms in childhood combine both positive and negative symptoms. Positive symptoms, such as hallucinations and delusions, are usually easy to identify. Negative symptoms, such as social withdrawal and thought disorder, may be harder to assess (Kendhari et al., 2016; Preti et al., 2012). Two recent studies have focused on early psychotic symptoms and have contributed to the description of two profiles resembling adult schizophrenia (Craddock et al., 2018; Giannitelli et al., 2020): a profile with high positive symptoms, i.e. hallucinations and delusions, and low negative symptoms, i.e., social withdrawal, thought disorder and anhedonia, and the opposite profile. The bizarre positive symptoms (first-rank symptoms and severity of hallucinations) highlighted by Giannitelli et al. (2020) have made it possible to emphasize specific characteristics which inevitably attract attention as potential markers of the severity and chronicity of psychotic disorders, especially when onset takes place before the age of 13 years.

In parallel with the conceptualization of COS, and based on the need to detect and treat the disease as early as possible, the construct of a clinical high-risk state for psychosis known as the Ultra-High-Risk (UHR) state were gradually developed in adult samples (Klosterkötter et al., 2001; Phillips et al., 2000; Schultze-Lutter et al., 2016; Yung et al., 1998) and children and adolescents (Schultze-Lutter et al., 2022). In the UHR approach, different symptoms were described: (i) attenuated psychotic symptoms, (ii) brief limited intermittent psychotic episode and (iii) genetic risk and deterioration (Fusar-Poli et al., 2013). According to meta-analyses, only the first two symptoms have sufficient predictive validity for psychosis (Fusar-Poli et al., 2016; Schultze-Lutter et al., 2015). Moreover, these criteria do not seem to have any predictive power for psychosis in children and adolescents since some symptoms may be present but without any clearly defined links to future symptomatology (Schultze-Lutter et al., 2022).

* Corresponding author at: Centre de Référence Maladies Rares Troubles du Comportement d'Origine Génétique (GénoPsy Lyon), Centre d'excellence Autisme iMIND, Centre Hospitalier Le Vinatier, UMR 5229, CNRS & Université Lyon 1, 95 Boulevard Pinel, Bron 69500, France.
*E-mail address:* marie-noelle.babinet@ch-le-vinatier.fr (M.-N. Babinet).

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There are very few studies on the incidence of childhood early psychotic symptoms (i.e., COS). One estimate by the National Institute of Mental Health (NIMH) is that the prevalence of COS is less than 0.04% (Driver et al., 2013; McClellan and Werry, 1997; McKenna et al., 1994), and 2% of adult cases have an estimated age at onset earlier than 13 (Schneider et al., 2015). Concerning the UHR approach in a child and adolescent population, the prevalence seems to depend on the tool used to screen for symptoms and, thus, varies from 1 to 8% (Fusar-Poli et al., 2013).

Genetic risk has been said to be an integral part of the symptomatology of people at high risk for psychosis (Fusar-Poli et al., 2013, 2016; Schultze-Lutter et al., 2015, 2016, 2022). Indeed, research has shown the role played by genetics as well as the environment in the development of childhood early psychotic symptoms (McClellan and Stock, 2013). Developing the disorder at an early age is a negative prognostic, and the phenotype may be more severe. If a first-degree relative has the disorder, the risk of developing it is 5 to 20 times higher than it is in the general population (McClellan and Stock, 2013). Patients with childhood early psychotic symptoms also have higher rates of cytogenetic abnormalities, such as 22q11.2 deletion syndrome (also known as velocardiofacial syndrome or DiGeorge syndrome, 22q11.2DS) (Jolin et al., 2009; Murphy et al., 1999; Sporn et al., 2004; Stoddard et al., 2010). Conversely, approximately 30% of patients with 22q11.2DS develop psychotic symptoms in adolescence or early adulthood (Monks et al., 2014).

It is important to note that not every child who has psychotic symptoms develops schizophrenia. Psychotic symptoms may be common among children with mood disorders or a history of trauma, as well as among those using illicit substances. It is also critical to rule out other medical causes of psychotic symptoms (McClellan, 2018). Unlike adults, children have developmentally normal behaviors that can be misconstrued as psychotic, such as having an imaginary friend (McClellan, 2018).

### 1.2. Childhood investigations and psychotic symptoms

Despite this noteworthy prevalence, few screening assistance tools exist, even though accurate and early diagnosis is important in order to treat children as early as possible and improve their future quality of life (McClellan, 2018). To date, the majority of childhood investigations have used the DSM criteria to identify psychotic symptoms. Two longitudinal studies have demonstrated moderate diagnostic stability across one-, two-, and three-year follow-up periods (Asarnow, 2005; Esterberg et al., 2010). A second approach used to identify children with schizotypal traits is to adapt adult measures of Schizotypy for use with children. This is the case of the Schizotypal Personality Questionnaire-Child (SPQ-C) (Ericson et al., 2011; Liu et al., 2019), the Schizotypy Traits Questionnaire-Child (STA-C) (Cyhlarova and Claridge, 2005), the Structured Interview for Prodromal Syndromes (SIPS) (Miller et al., 2003) and the Prodromal Questionnaire (PQ) (Loewy et al., 2005) adapted from the Schizotypal Personality Questionnaire – adult version (SPQ) (Raine, 1991). The SPQ-C is based on the DSM-IV criteria for Schizotypal Personality Disorder (SPD) and comprises three factors: cognitive/perceptual difficulties, interpersonal difficulties, and disorganized symptoms (Ericson et al., 2011). In contrast, the STA-C assesses the positive symptoms of Schizotypy, i.e. unusual perceptual experiences, paranoid ideation/social anxiety, and magical thinking (Cyhlarova and Claridge, 2005). The SIPS is a structured interview used to diagnose the three prodromal syndromes, i.e. (i) frankly psychotic positive symptoms that appeared too brief and too intermittent to constitute a fully psychotic syndrome, (ii) attenuated positive symptoms and (iii) functional decline in the presence of genetic risk, and may be thought of as analogous to the Structured Clinical Interview for DSM-IV or other structured diagnostic interviews (Miller et al., 2003). In general, the PQ, a 92-item self-report, assesses (i) positive symptoms, (ii) negative symptoms, (iii) disorganized symptoms and (iv) general symptoms (Loewy et al., 2005). Furthermore, the adapted scales are based on adult personality disorders and do not include observational data and informant reports, which are recommended for assessing childhood personality traits (Tackett, 2010). To overcome these methodological issues, Jones and colleagues (Jones et al., 2015) developed the Melbourne Assessment of Schizotypy in Kids (MASK), a semi-structured assessment designed to capture the clinical features of childhood SPD. This tool gathers information from three sources to describe symptomology: the parent, the child, and observations by the treating clinician. Items on the MASK are largely based on DSM-IV criteria but also assess features of childhood SPD, including motor deficits and bizarre fantasies.

### 1.3. Interest of a new scale assessing early psychotic symptoms

Although the MASK is an interesting assessment tool because it comes from three sources and includes the characteristics of childhood SPD, the length of the assessment (57 items) can be an obstacle to its administration. Indeed, asking children's opinions involves several methodological problems. First, there are competence issues: are the children competent to understand and answer the questions addressed to them? This raises the question of whether it is relevant to survey children directly at all (Pagis and Simon, 2020). Second, children are often perceived as beings who regularly change their minds, without being certain of their opinions (Vaillancourt, 1973), and this casts doubt on the stability and reliability of their responses. We can, finally, ask whether children are aware of their own symptoms. To avoid such issues, we have developed a new scale, which is faster to administer and is completed by the child's parents. The scale comes in two versions: assessment of the child's current behavior and assessment of behavior when the child was 2 years old. Evaluating behavior at the age of 2 years makes it possible to estimate whether the targeted symptoms were already present at that time. Thus, from a fundamental point of view, the scale helps reveal the development of the child's symptoms. This methodology can be questioned because of possible memory biases, but it is based on existing scales (Frigaux et al., 2019; Lord et al., 1994).

The aim of this study is thus two-fold: (i) to develop a screening tool for childhood early psychotic symptoms, (ii) to investigate the presence of these symptoms at the age of 2 years and in the present. To this end, two studies will be presented (1) the psychometric validation of the scale and (2) an inter-group comparison.

## 2. Method

### 2.1. Study 1: validation of the scale

#### 2.1.1. Participants

Two hundred and forty parents of normo-typical children aged 4 to 13 (M = 8.82; SD = 2.89; girls = 119; boys = 121) were recruited through phone calls, social networks and ordinary mail. Recruitment was initiated by friends, colleagues and siblings of children seen in consultation at the Center of Rare Diseases Reference, GénoPsy, in Lyon (France). Subsequently, recruitment took place through a snowball effect. For inclusions, any parent of a normo-typical child aged 4 to 13 years was recruited. The only exclusion criterion was the presence of significant comorbid medical conditions, such as history of neurological disorders affecting the cerebral function. Each parent signed informed consent. The study was conducted in accordance with the Declaration of Helsinki and was approved by the national Ethics Committee (CPP Est-II, No. 2020-A01370–39; NCT04639388).

#### 2.1.2. Measures

*The scale.* The Early Psychotic Symptoms screening scale (EPSy) is a scale developed to assess the prodromes of psychotic symptoms in children aged 4 to 13 years. The questions were developed based on

several sources, including questionnaires measuring schizotypal traits in children (The Melbourne Assessment Schizotypy in Kids, MASK, Jones et al. (2015)) and child anxiety (The Screen for Child Anxiety Related Emotional Disorders, SCARED, Birmaher et al. (1997)), as well as on interviews with families of patients and professionals (psychiatrists, child psychiatrists, psychologists, nurses) who are experts in childhood psychiatric disorders. After analyzing the above questionnaires and interviews, we identified various behaviors of interest which it appeared essential to include in the scale: hallucinations, paranoia / persecution, atypical fears / anxiety, disorganized behavior, emotional difficulties. First of all, nineteen questions were developed, 4 of which related to persecution / paranoia, 3 to hallucinations, 5 to disorganized behavior, 3 to atypical fears / anxiety, and 4 to emotional difficulties (see Table 1, Version 1). A discussion with expert professionals was undertaken to identify the extent to which the items corresponded to clinical reality. During a second step, item 1 "Has changed behavior" was deemed to be insufficiently specific and was therefore removed. Conversely, it was considered necessary to add a new item: " Tends to misinterpret it when other people look at him." During the third stage, several modifications were made and items added based on the families' comments. For example, the item " Tends to confuse the imaginary and the real." was transformed into " Does not distinguish between the stories he tells and reality.", and other items were added, like " Makes incongruous or inappropriate facial expressions when interacting with others" (see other modifications in Table 1).

In all, 24 questions were developed (see Table 1) and two versions of each of these were proposed: one to assess the child's current behavior and one to assess the child's behavior when he/she was 2 years old. To answer the "age 2 questions", the parents had to think back and recall their child's behavior at that age (Lord et al., 1994). This method was used to identify whether psychotic symptoms were already present as early as age 2. Also, the two versions of the scale were used to find out whether behavior at age 2 predicted the child's current behavior. Each item was rated on a Likert scale (0: This behavior is absent; 1: This behavior is present and it is not at all a problem; 2: This behavior is present and it is a minor problem; 3: This behavior is present and it is a major problem). The choice of ratings was inspired by the Aberrant Behavior Checklist (ABC, Aman and Singh (1986)), which is frequently used in clinical settings. The rating we propose is based on the presence of problematic behavior and its impact on daily life. Parents were asked not to spend too much time on each question because the first reaction is usually the right one. The higher the score, the more present and problematic the symptomatology is reported to be by the parents. It takes approximatively 10 min to complete the scale.

*Convergent validity*. The interest that has been shown in neurodevelopmental disorders and their potential associated disorders enabled us to find scales for the assessment of convergent validity. Indeed, recent interest in the neurodevelopmental trajectories of schizophrenia spectrum disorders has led to various observations, in particular the fact that there is relatively consistent evidence that children who later develop schizophrenia have behavioral disturbances, such as aggressive characteristics (Raine et al., 2011), schizotypal disorders, cognitive and attentional deficits, symptoms of social anxiety and symptoms of separation anxiety (Welham et al., 2009).

Several existing scales designed to document specific problematic behaviors in children with developmental disorders were administered in order to assess the convergent validity of the EPSy. The MASK (Jones et al., 2015), a 57-item semi-structured questionnaire, measures SPD characteristics in children aged 5 to 12 years. It assesses social/-pragmatic symptoms and positive schizotypal symptoms. Each item is rated on a Likert Scale (1=Never; 2=Sometimes; 3= Often; 4=Always). Aggressive behavior was assessed with the reactive-proactive aggression questionnaire (Dodge and Coie, 1987; Poulin and Boivin, 2000), a 6-item questionnaire using a 5-point Likert scale (0 = never; 5 = almost always). The higher the score, the more aggressive the child is described as being by his/her parents. The Conners Parent Rating Scale-48 items (CPRS) (Catale et al., 2014; Conners, 1969; Dugas et al., 1987) is one of the behavioral scales most frequently used in clinical and research settings with children suffering from neurodevelopmental disorders. It is a 48-item questionnaire measuring children's behaviors or the problems they sometimes have, such as attention disorders. This questionnaire uses a 4-point Likert scale (0 = never; 4 = almost always). The current study also used three DSM-V diagnostic criteria (American Psychiatric Association, 2013) for Attention-Deficit Hyperactivity Disorder (ADHD), Social anxiety and Separation anxiety. Participants must answer yes or no to each item.

#### 2.1.3. Procedure

Two hundred and forty parents of normo-typical children aged 4 to 13 completed the scales and questionnaires in the following order: (i) current-age version of the EPSy screening scale, (ii) 2-years-old version of the EPSy screening scale, (iii) the reactive-proactive aggression questionnaire, (iv) the MASK, (v) DSM-V: ADHD; DSM-V: Social anxiety; and DSM-V: Separation anxiety and (vi) the CPRS-48. Data were collected over a period of one year. Forty-eight parents completed the scales in paper format, and one hundred and ninety-two parents completed the digital format, i.e., by responding to an online questionnaire.

To assess test-retest reliability, a subgroup of fifty parents completed the two versions of the EPSy screening scale again one year after first responding to it (m = 12.36 months, SD = 0.8 months, min = 11 months, max = 14 months). A period of one year is sufficient for assessing test-retest reliability, that is, to see how parents describe similar situations.

#### 2.1.4. Statistical analyses

Data were analyzed using JASP software (JASP Team, 2022) and several analyses were undertaken: (i) The structure of the EPSy was analyzed by means of an Exploratory Factor Analysis (EFA) using principal axis extraction with an orthogonal varimax rotation. Loadings were considered if they were equal to or greater than 0.30, and factors were considered only if their eigenvalue was equal to or greater than 1; (ii) Internal consistency was examined through Cronbach's alpha coefficients; (iii) Convergent validity was assessed on the basis of Pearson correlation coefficients between the EPSy and raw subscale scores from the MASK, the reactive-proactive aggression questionnaire, the Conners scale and DSM-V ADHD; DSM-V; Social anxiety; and DSM-V: Separation anxiety; (iv) A multiple linear regression analysis was conducted to assess whether EPSy scores for the child's 2nd year of life predicted the scores in the current-age version of the questionnaire, and the child's age at the time the scale was completed was also included as a predictor. This regression was used to find out whether the number of years the parents had to go back in time to recall their child's behavior had an influence on the way the scale was completed; (v) Finally, one-year test-retest reliability was assessed through Pearson correlation coefficients.

### 2.2. Study 2: group differences

The scale was also used to compare three groups of children, namely psychotic children, non-psychotic children and controls. The objective was to investigate possible differences in symptomatology and to observe any changes in this symptomatology between the age of 2 and the age at completion of the current-age scale.

#### 2.2.1. Participants

The parents of one hundred and seventeen children aged between 4 and 13 years (M = 9.86; SD = 2.6) were asked to complete the EPSy screening scale. Children were assigned to one of three groups: psychotic children ($n = 17$), non-psychotic children ($n = 22$) and controls (n = 78). Psychotic and non-psychotic children were recruited through the Center

**Table 1**
Construction of the EPSy scale items.

| **Version 1** | | **Version 2** | | **Version 3** | |
|---|---|---|---|---|---|
| French Version | English Version | French Version | English Version | French Version | English Version |
| 1. A changé de comportement. | 1. Has changed behavior. | 1. A des idées, des croyances qui semblent inhabituelles ou bizarres. | 1. Has ideas, beliefs that seem unusual or weird. | 1. A des idées, des croyances qui semblent inhabituelles ou bizarres. | 1. Has ideas, beliefs that seem unusual or weird. |
| 2. A des idées, des croyances qui semblent inhabituelles ou bizarres. | 2. Has ideas, beliefs that seem unusual or bizarre. | 2. A tendance à confondre l'imaginaire et le réel. | 2. Tends to confuse the imaginary and the real. | *2. Ne distingue pas les histoires qu'il raconte et la réalité.* | *2. Does not distinguish between the stories he tells and reality.* |
| 3. A tendance à confondre l'imaginaire et le réel. | 3. Tends to confuse the imaginary and the real. | 3. Pense que les gens autour de lui ont l'intention de lui faire du mal. | 3. Thinks that the people around him intend to hurt him. | *3. A l'impression que les gens autour de lui ont l'intention de lui faire du mal.* | *3. Feels like people around him intend to hurt him.* |
| 4. Pense que les gens autour de lui ont l'intention de lui faire du mal. | 4. Thinks that the people around him intend to hurt him. | 4. Est méfiant envers les autres. | 4. Is suspicious of others. | *4. Est méfiant envers les autres ou face à des situations.* | *4. Is suspicious of others or of situations.* |
| 5. Est méfiant envers les autres. | 5. Is suspicious of others. | 5. A l'impression que les autres se moquent de lui. | 5. Thinks that other people are laughing at him. | 5. A l'impression que les autres se moquent de lui. | 5. Thinks that other people are laughing at him. |
| 6. A l'impression que les autres se moquent de lui. | 6. Thinks that others are laughing at him. | 6. A peur de dormir sans lumière/dans le noir. | 6. Is afraid to sleep without the light on / in the dark. | 6. A peur de dormir sans lumière/dans le noir. | 6. Is afraid to sleep without the light on / in the dark. |
| 7. A peur de dormir sans lumière/dans le noir. | 7. Is afraid of sleeping without the light on / in the dark. | 7. Vous a déjà parlé de choses qu'il voit ou entend dans la nuit. | 7. Has told you about things he sees or hears at night. | 7. A déjà parlé de choses qu'il voit ou entend dans la nuit. | 7. Has spoken about things he sees or hears at night. |
| 8. Vous a déjà parlé de choses qu'il voit ou entend dans la nuit. | 8. Has told you about things he sees or hears at night. | 8. A un discours désorganisé qui vous empêche de suivre le fil conducteur. | 8. Has disorganized speech that prevents you from following what he is talking about. | *8. A un discours confus qui empêche son interlocuteur de suivre le fil conducteur et de comprendre le récit.* | *8. Has confused speech that prevents the person he is talking to from following what he is talking about and understanding him.* |
| 9. A un discours désorganisé qui vous empêche de suivre le fil conducteur. | 9. Has disorganized speech that prevents you from following what he is talking about. | 9. A une tendance à l'isolement que ce soit dans la cour de récréation ou bien en dehors de l'école. | 9. Has a tendency to be isolated whether in the playground or outside of school. | 9. A une tendance à l'isolement que ce soit dans la cour de récréation ou bien en dehors de l'école. | 9. Has a tendency to be isolated whether in the playground or outside of school. |
| 10. A une tendance à l'isolement que ce soit dans la cour de récréation ou bien en dehors de l'école. | 10. Has a tendency to be isolated whether in the playground or outside of school. | 10. A des difficultés pour reconnaître les émotions des autres. | 10. Has difficulty recognizing other people's emotions. | *10. Se comporte de façon inadaptée face aux émotions des autres faisant penser qu'il ne les comprend pas.* | *10. Reacts inappropriately to other people's emotions, making them think he does not understand them.* |
| 11. A des difficultés pour reconnaître les émotions des autres. | 11. Has difficulty recognizing the emotions of others. | 11. A des difficultés à gérer ses propres émotions. | 11. Has difficulty dealing with his own emotions. | 11. A des difficultés pour gérer ses propres émotions. | 11. Has difficulty dealing with his own emotions. |
| 12. A des difficultés à gérer ses propres émotions. | 12. Has difficulty dealing with his own emotions. | 12. A tendance à ne pas regarder les gens dans les yeux, à fuir le regard des autres. | 12. Tends not to look people in the eye, to avoid the gaze of others. | 12. A tendance à ne pas regarder les gens dans les yeux, à fuir le regard des autres. | 12. Tends not to look people in the eye, to avoid the gaze of others. |
| 13. A tendance à ne pas regarder les gens dans les yeux, à fuir le regard des autres. | 13. Tends not to look people in the eye, to avoid the gaze of others. | *13. A tendance à mal interpréter un regard dirigé vers lui.* | *13. Tends to misinterpret it when other people look at him.* | *13. Se comporte de façon inadaptée lorsqu'un regard est dirigé vers lui comme s'il l'interprétait mal.* | *13. Behaves inappropriately when people look at him, as if he is misinterpreting them.* |
| 14. A des difficultés à comprendre l'humour, l'ironie ou les sous-entendus. | 14. Has difficulty understanding humor, irony or innuendo. | 14. A des difficultés à comprendre l'humour, l'ironie ou les sous-entendus. | 14. Has difficulty understanding humor, irony or innuendo. | **14. Manifeste des expressions faciales incongrues ou inappropriées en réponse à une interaction.** | **14. Makes incongruous or inappropriate facial expressions when interacting with others.** |
| 15. Est anxieux. | 15. Is anxious. | 15. Est anxieux. | 15. Is anxious. | **15. Sa voix présente des intonations inhabituelles (ex. voix monotone, absence de rythme dans son discours, ne modifie pas le volume de sa voix en fonction de l'endroit ou de la situation).** | **15. His speech contains unusual intonations (e.g. monotonous voice, lack of rhythm in his speech, does not change the volume of his voice depending on the place or the situation).** |
| 16. Est stressé, désorganisé dans son comportement. | 16. Is stressed, disorganized in his behavior. | 16. Est stressé, désorganisé dans son comportement. | 16. Is stressed, disorganized in his behavior. | 16. A des difficultés à comprendre l'humour, l'ironie ou les sous-entendus. | 16. Has difficulty understanding humor, irony or innuendo. |
| 17. Semble voir ou entendre des choses que les autres ne voient pas. | 17. Seems to see or hear things that others cannot see. | 17. Semble voir ou entendre des choses que les autres ne voient pas. | 17. Seems to see or hear things that others cannot see. | 17. Est anxieux, stressé. | 17. Is anxious, stressed. |

(*continued on next page*)

**Table 1** (*continued*)

| Version 1 | | Version 2 | | Version 3 | |
|---|---|---|---|---|---|
| French Version | English Version | French Version | English Version | French Version | English Version |
| 18. Semble effrayé ou paniqué dans des situations anodines. | 18. Appears scared or panicked by trivial situations. | 18. Semble effrayé ou paniqué dans des situations anodines. | 18. Appears scared or panicked by trivial situations. | 18. Est désorganisé dans son comportement. | 18. Is disorganized in his behavior. |
| 19. Coupe la parole, suit son idée, fait des digressions avec l'impression qu'il ne s'intéresse pas à son interlocuteur. | 19. Interrupts others when they are talking, pursues his own thoughts, digresses, giving the impression that he is not interested in the person he is talking to. | 19. Coupe la parole, suit son idée, fait des digressions avec l'impression qu'il ne s'intéresse pas à son interlocuteur. | 19. Interrupts others when they are talking, pursues his own thoughts, digresses, giving the impression that he is not interested in the person he is talking to | 19. Semble voir ou entendre des choses que les autres ne voient pas. | 19. Seems to see or hear things that others cannot see. |
| | | | | 20. Semble effrayé ou paniqué dans des situations anodines. | 20. Appears scared or panicked by trivial situations. |
| | | | | 21. Coupe la parole, suit son idée, fait des digressions donnant l'impression qu'il ne s'intéresse pas à son interlocuteur. | 21. Interrupts others when they are talking, pursues his own thoughts, digresses, giving the impression that he is not interested in the person he is talking to. |
| | | | | **22. Se montre méfiant de manière inexpliquée ou inhabituelle à l'égard d'événements ou de personnes** | **22. Is inexplicably or unusually suspicious of events or people** |
| | | | | **23. Parle de sons, de visions, d'odeurs ou de sensations exacerbés, altérés ou bizarres** | **23. Talks about intensified, impaired or bizarre sounds, sights, smells or sensations** |
| | | | | **24. Fait part d'odeurs ou de sensations tactiles qui ne sont pas basées sur la réalité** | **24. Reports odors or tactile sensations that do not correspond to reality** |

*Note*: Items in italics: modified items; items in bold: added items.

of Rare Diseases Reference, GénoPsy, in Lyon (France). The study procedure was proposed together with routine care (medical and neuropsychological consultations), so that the diagnosis of psychosis was discussed within the framework of their overall care at GénoPsy, but not specifically for the study. Any child with a neurodevelopmental disorder associated with behavioral disorders and/or psychiatric disorders was included. Children were excluded from the study if they had significant comorbid medical conditions, such as the presence or history of neurological disorders affecting the cerebral function. If the genetic origin was known, the diagnosis was confirmed in all patients by fluorescence *in situ* hybridization (FISH) and complete genomic hybridization (CHG-Array). Children were assigned to their respective group on the basis of an interview (see Procedure section). Controls were selected from among those who had participated in Study 1 and were matched on age and gender with the other two groups (Table 2). Both parents signed informed consent. The study was conducted in accordance with the Declaration of Helsinki and was approved by a national Ethics Committee (CPP Est-II, No. 2020-A01370–39; NCT04639388).

### 2.2.2. Procedure

Parents completed the current-age version of the EPSy screening scale, followed by the 2-years-old version. In the case of children with a neurodevelopmental disorder, the Psychosis section of the French version of the K-SADS-PL screening interview (Thümmler and Askenazy, 2018) was proposed by a doctor to the family group (parent and child). During this session, two main topics were addressed by the doctor: (i) auditory and visual hallucinations and (ii) delusions. For each topic, the doctor assessed whether the symptoms were absent (scored 1), subclinical, i.e., suspected or probable symptoms (scored 2), or clinical, i.e., presence of some of the symptoms (scored 3). Subsequently, if a

**Table 2**
Descriptive statistics for age and gender for each experimental group.

| Variable | Psychotic children (n = 17) | Non-psychotic children (n = 22) | Controls (n = 78) | Group differences |
|---|---|---|---|---|
| % Female | 47% | 50% | 47,4% | $X^2(2) = 0.05$, $p = .98$ |
| Mean (SD) Age in years | 9.92 (2.89) | 9.76 (2.52) | 9.84 (2.58) | $F(2114) = 0.01$, $p = .99$ |
| Genetic diagnosis (N (%)) | 22q11.2DS (10 (58%)) | 22q11.2DS (15 (68%)) | | |
| | Triple X syndrome (3 (18%)) | Coffin-Siris syndrome (ARID1B mutation) (1 (4%)) | | |
| | 16p13.11DS (2 (12%)) | Williams-Beuren syndrome (3 (14%)) | | |
| | Klinefelter syndrome (1 (6%)) | Smith-Magenis syndrome (3 (14%)) | | |
| | 15q13.3DS (1 (6%)) | | | |
| Comorbidities (N (%)) | ADHD (6 (35%)) | ADHD (8 (36%)) | | |
| Treatment at time of assessment (N (%)) | Neuroleptic (5 (29%)) | Methylphenidate (3 (14%)) | | |
| | SSRI (1 (6%)) | | | |
| | Methylphenidate (2 (12%)) | | | |
| Education level (N (%)) | Kindergarten (2 (12%)) | Primary school (13 (59%)) | | |
| | Primary school (10 (59%)) | Secondary school (3 (14%)) | | |
| | Secondary school (5 (29%)) | Medico-social (6 (27%)) | | |

*Note*: DS = deletion syndrome; SSRI = Selective Serotonin Reuptake Inhibitor; ADHD = Attention Deficit Hyperactivity Disorder

score of 3 was obtained for one of the two above-mentioned topics, this meant that there was a strong possibility of Schizophrenia Spectrum Disorder (SSD) and the child was thus assigned to the psychotic group.

### 2.2.3. Statistical analysis

Given the heterogeneity of the number of items per factor, the mean score was used. The mean score on the EPSy screening scale was analyzed using a mixed analysis of variance (ANOVA, $\alpha = 0.05$, throughout) with the scale version (2-years-old version vs. current-age version) and the subscales (mistrust, hallucinations, disorganization) as within-participants factors, and the group (controls, non-psychotic and psychotic) as between-participants factor. The Greenhouse–Geisser sphericity correction was applied whenever necessary. Partial eta-squared ($\eta_p^2$) coefficients were used to express effect sizes. Multiple post-hoc comparisons were conducted using the Holm test. Statistics were computed using JASP (JASP Team, 2022).

## 3. Results

### 3.1. Study 1: validation of the scale

#### 3.1.1. EPSy screening scale factors

We used the current-age version of the scale for the EFA, given that current behavior is more significant and thus makes it possible to highlight factors that can be retrospectively examined at the age of 2 years in order to determine the extent to which the factors were already present at that age. An initial principal axis analysis (eigenvalues greater than 1) revealed three factors that explained 37.4% of the variance. Twelve items (Items 3, 4, 5, 9, 10, 11, 12, 13, 16, 17, 20 and 22) loaded on a first factor, which explained 14% of the variance and represented mistrust/paranoia. Five items (Items 1, 7, 19, 23 and 24) loaded on a second factor, which explained 6.8% of the variance and represented perceptual aberrations/hallucinations. Five items (Items 2, 8, 15, 18 and 21) loaded on a third factor, which explained 16.6% of the variance and represented disorganized behavior. Two items (Items 6 and 14) did not load on either factor (Table 3). This may be indicative of a lack of sensitivity and they were therefore dropped. In total, 22 items were retained. A confirmatory factor analysis was conducted on the 2-years-old version since the objective was to find out whether current factors were predicted by the factors at age 2. The 3-factor model of the current-age version seems to apply to the 2-years-old version ($\chi^2(206) = 1171$, $\chi^2/df = 5.68$, $CFI = 0.66$, $TLI = 0.62$, $RMSEA = 0.14$, $SRMR = 0.11$, $AIC = 5142$, $GFI = 0.68$, $MFI = 0.13$). These results testify of a rather good fit, even if it is not perfect.

For the 2-years-old version of the scale, the average of the total scores was 5.50, the standard deviation is 6.47 and the 9th decile was 11. For each factor, the data were as follows: Factor 1 (mistrust-paranoia): m = 3.75; SD = 4.14; Factor 2 (perceptual aberrations / hallucinations): m = 0.65; SD = 1.86; Factor 3 (disorganization): m = 1.10; SD = 1.50.

For the current-age version of the scale, the average of the total scores was 5.23, the standard deviation was 5.44 and the 9th decile was 9. For each factor, the data were as follows: Factor 1 (mistrust-paranoia): m = 3.53; SD = 3.72; Factor 2 (perceptual aberrations / hallucinations): m = 0.70; SD = 1.49; Factor 3 (disorganization): m = 1.01; SD = 1.53.

#### 3.1.2. Internal consistency

For the 2-years-old version, the Cronbach alpha coefficient for the total score on the EPSy was 0.90. Alpha coefficients for the three factors were 0.84 for mistrust/paranoia, 0.89 for perceptual aberrations/hallucinations, and 0.65 for disorganization.

For the current-age version, the Cronbach alpha coefficient for the total score on the EPSy was 0.85. Alpha coefficients for the three factors were 0.80 for mistrust/paranoia, 0.76 for perceptual aberrations/hallucinations, and 0.65 for disorganization.

For both versions of the scale, significant correlations were observed between the total score and the score on each factor, as well as between

**Table 3**
Orthogonally rotated factor loadings on three schizotypal factors from the current-age version scale.

| Item number | French version | English version | Factor 1 | Factor 2 | Factor 3 |
|---|---|---|---|---|---|
| 1 | A des idées, des croyances qui semblent inhabituelles ou bizarres | Has ideas, beliefs that seem unusual or weird | | 0.449 | |
| 2 | Ne distingue pas les histoires qu'il raconte et la réalité | Does not distinguish between the stories he tells and reality | | | 0.369 |
| 3 | A l'impression que les gens autour de lui ont l'intention de lui faire du mal | Feels like people around him intend to hurt him | 0.673 | | |
| 4 | Est méfiant envers les autres ou face à des situations | Is suspicious of others or of situations | 0.633 | | |
| 5 | A l'impression que les autres se moquent de lui | Thinks that other people are laughing at him | 0.500 | | |
| 6 | A peur de dormir sans lumière/ dans le noir | Is afraid to sleep without the light on / in the dark | | | |
| 7 | A déjà parlé de choses qu'il voit ou entend dans la nuit | Has spoken about things he sees or hears at night | | 0.380 | |
| 8 | A un discours confus qui empêche son interlocuteur de suivre le fil conducteur et de comprendre le récit | Has confused speech that prevents the person he is talking to from following what he is talking about and understanding him | | | 0.662 |
| 9 | A une tendance à l'isolement que ce soit dans la cour de récréation ou bien en dehors de l'école | Has a tendency to be isolated whether in the playground or outside of school | 0.565 | | |
| 10 | Se comporte de façon inadaptée face aux émotions des autres faisant penser qu'il ne les comprend pas | Reacts inappropriately to other people's emotions, making them think he does not understand them | 0.349 | | |
| 11 | A des difficultés pour gérer ses propres émotions | Has difficulty dealing with his own emotions | 0.511 | | |
| 12 | A tendance à ne pas regarder les gens dans les yeux, à fuir le regard des autres | Tends not to look people in the eye, to avoid the gaze of others | 0.476 | | |
| 13 | Se comporte de façon inadaptée lorsqu'un regard est dirigé vers lui comme s'il l'interprétait mal | Behaves inappropriately when people look at him, as if he is misinterpreting them | 0.734 | | |
| 14 | Manifeste des expressions faciales incongrues ou inappropriées en | Makes incongruous or inappropriate facial expressions | | | |

(continued on next page)

**Table 3** (*continued*)

| Item number | French version | English version | Factor 1 | Factor 2 | Factor 3 |
|---|---|---|---|---|---|
| | réponse à une interaction | when interacting with others | | | |
| 15 | Sa voix présente des intonations inhabituelles (ex. voix monotone, absence de rythme dans son discours, ne modifie pas le volume de sa voix en fonction de l'endroit ou de la situation) | His speech contains unusual intonations (e.g. monotonous voice, lack of rhythm in his speech, does not change the volume of his voice depending on the place or the situation) | | | 0.453 |
| 16 | A des difficultés à comprendre l'humour, l'ironie ou les sous-entendus | Has difficulty understanding humor, irony or innuendo | 0.407 | | |
| 17 | Est anxieux, stressé | Is anxious, stressed | 0.436 | | |
| 18 | Est désorganisé dans son comportement | Is disorganized in his behavior | | | 0.481 |
| 19 | Semble voir ou entendre des choses que les autres ne voient pas | Seems to see or hear things that others cannot see | | 0.879 | |
| 20 | Semble effrayé ou paniqué dans des situations anodines | Appears scared or panicked by trivial situations | 0.354 | | |
| 21 | Coupe la parole, suit son idée, fait des digressions donnant l'impression qu'il ne s'intéresse pas à son interlocuteur | Interrupts others when they are talking, pursues his own thoughts, digresses, giving the impression that he is not interested in the person he is talking to | | | 0.532 |
| 22 | Se montre méfiant de manière inexpliquée ou inhabituelle à l'égard d'événements ou de personnes | Is inexplicably or unusually suspicious of events or people | 0.606 | | |
| 23 | Parle de sons, de visions, d'odeurs ou de sensations exacerbés, altérés ou bizarres | Talks about intensified, impaired or bizarre sounds, sights, smells or sensations | | 0.950 | |
| 24 | Fait part d'odeurs ou de sensations tactiles qui ne sont pas basées sur la réalité | Reports odors or tactile sensations that do not correspond to reality | | 0.780 | |

*Note.* Factor 1: mistrust/paranoia symptoms; Factor 2: perceptual aberrations/hallucinations symptoms; Factor 3: disorganization symptoms.

the factors and between each item and its membership factor (see Tables 4 and 5; all $r > 0.315$ and all $ps < .05$).

### 3.1.3. Convergent validity

Significant correlations were observed between the scale (current-age version and 2-years-old version), each of the factors and the MASK, the reactive-proactive aggression questionnaire, the Conners scale and the DSM-V criteria (see Table 6), indicating satisfactory convergent validity (all $r > 0.127$, all $ps < .05$).

The regression analysis showed that the total score on the 2-years-old version significantly predicted the total score on the current-age version of the scale ($F(2237) = 197.4$, $p < .001$, $R^2 = 0.63$; $\beta = 0.79$; SEM = 0.03; $t(239) = 19.9$, $p < .001$). Age had no effect.

The regression analysis showed that mistrust/paranoia on the 2-years-old scale predicted mistrust/paranoia on the current scale ($F(2237) = 152.4$, $p < .001$, $R^2 = 0.56$; $\beta = 0.67$; SEM = 0.04; $t(239) = 17.4$, $p < .001$). This was also the case for perceptual aberrations/hallucinations ($F(2237) = 177$, $p < .001$, $R^2 = 0.67$); $\beta = 0.66$; SEM = 0.03; $t(239) = 21.9$, $p < .001$) and disorganization $F(2237) = 44.2$, $p < .001$, $R^2 = 0.27$; $\beta = 0.53$; SEM = 0.06; $t(239) = 9.3$, $p < .001$).

### 3.1.4. One-year test-retest reliability

The one-year test-retest Pearson correlation coefficient was 0.99 for the 2-years-old version of the scale. Pearson correlation coefficients for the three factors were 0.99 for mistrust/paranoia, 0.99 for perceptual aberrations/hallucinations, and 0.98 for disorganization. All $ps < .001$.

For the current-age version, the one-year test-retest Pearson correlation coefficient was 0.99 ($CI_{95\%}$: 0.98 .. 0.99, $p < .001$). Pearson correlation coefficients for the three factors were 0.97 for mistrust/paranoia, 0.99 for perceptual aberrations/hallucinations, and 0.97 for disorganization. All $ps < .001$.

## 3.2. Study 2: group differences

A significant group*scale version*subscales interaction was observed for the main score, $F(3195) = 7.44$, $p < .001$, $\eta_p^2$=0.12 (Fig. 1). As far as mistrust in the 2-years-old version was concerned, both psychotic children (mean = 1.48, SD = 0.76) and non-psychotic children (mean = 0.67, SD = 0.57) scored significantly higher than controls (mean = 0.24, SD = 0.17). Moreover, psychotic children scored higher than non-psychotic children (all $ps < .001$). Similar results were also found for the current-age version. Psychotic children (mean = 1.54, SD = 0.41) and non-psychotic children (mean = 0.69, SD = 0.42) scored significantly higher than controls (mean = 0.28, SD = 0.18). In addition, psychotic children scored higher than non-psychotic children (all $ps < .001$).

As far as hallucinations in the 2-years-old version were concerned, no significant differences were observed between the three groups (control group: mean = 0.09, SD = 0.16; non-psychotic children group: mean = 0.1, SD = 0.25; psychotic children group: mean = 0.37, SD = 0.72). However, in the current-age version, psychotic children (mean = 0.8, SD = 0.44) scored significantly higher than both controls (mean = 0.09, SD = 0.12) and non-psychotic children (mean = 0.12, SD = 0.18) (all $ps < .001$). No significant difference was observed between controls and non-psychotic children.

As far as disorganization in the 2-years-old version was concerned, both psychotic children (mean = 0.67, SD = 0.8) and non-psychotic children (mean = 0.53, SD = 0.59) scored significantly higher than controls (mean = 0.19, SD = 0.26). No significant difference was observed between non-psychotic and psychotic children. As far as the current-age version was concerned, psychotic children (mean = 1.3, SD = 0.71) and non-psychotic children (mean = 0.72, SD = 0.66) scored significantly higher than controls (mean = 0.13, SD = 0.2). Moreover, psychotic children scored higher than non-psychotic children (all $ps < .001$).

## 4. Discussion

The aim of this study was two-fold: (i) to develop a screening tool for childhood early psychotic symptoms and (ii) to investigate the presence of these symptoms at the age of 2 years and their evolution up to the child's current age. We therefore developed a scale suitable for use with

**Table 4**
Pearson correlation coefficients between the total score on the current-age version of the EPSy screening scale and each factor and also between factors and between each item and its membership factor.

| | | CURRENT-AGE Total score (*r*) | Factor 1: mistrust/ paranoia (*r*) | Factor 2: perceptual aberrations/ hallucination (*r*) | Factor 3: disorganization (*r*) |
|---|---|---|---|---|---|
| EPSy screening scale | **CURRENT-AGE Total score** | / | / | / | / |
| | **Factor 1 (mistrust/paranoia)** | 0.920*** | / | / | / |
| | Item 3 | / | 0.677*** | / | / |
| | Item 4 | / | 0.646*** | / | / |
| | Item 5 | / | 0.653*** | / | / |
| | Item 9 | / | 0.642*** | / | / |
| | Item 10 | / | 0.412*** | / | / |
| | Item 11 | / | 0.691*** | / | / |
| | Item 12 | / | 0.505*** | / | / |
| | Item 13 | / | 0.658*** | / | / |
| | Item 16 | / | 0.441*** | / | / |
| | Item 17 | / | 0.609*** | / | / |
| | Item 20 | / | 0.531*** | / | / |
| | Item 22 | / | 0.547*** | / | / |
| | **Factor 2 (perceptual aberrations/ hallucinations)** | 0.703*** | 0.480*** | / | / |
| | Item 1 | / | / | 0.638*** | / |
| | Item 7 | / | / | 0.733*** | / |
| | Item 19 | / | / | 0.837*** | / |
| | Item 23 | / | / | 0.880*** | / |
| | Item 24 | / | / | 0.760*** | / |
| | **Factor 3 (disorganization)** | 0.634*** | 0.373*** | 0.358*** | / |
| | Item 2 | / | / | / | 0.509*** |
| | Item 8 | / | / | / | 0.745*** |
| | Item 15 | / | / | / | 0.590*** |
| | Item 18 | / | / | / | 0.690*** |
| | Item 21 | / | / | / | 0.705*** |

Note. * p<.05, ** p<.01, ***p<.001

**Table 5**
Pearson correlation coefficients between the total score on the 2-years-old version of the EPSy screening scale and each factor and also between factors and between each item and its membership factor.

| | | 2-YEARS total score (*r*) | Factor 1: mistrust/ paranoia (*r*) | Factor 2: perceptual aberrations/ hallucination (*r*) | Factor 3: disorganization (*r*) |
|---|---|---|---|---|---|
| EPSy screening scale | **2-YEARS total score** | / | / | / | / |
| | **Factor 1 (mistrust/paranoia)** | 0.948*** | / | / | / |
| | Item 3 | / | 0.519*** | / | / |
| | Item 4 | / | 0.627*** | / | / |
| | Item 5 | / | 0.593*** | / | / |
| | Item 9 | / | 0.554*** | / | / |
| | Item 10 | / | 0.445*** | / | / |
| | Item 11 | / | 0.722*** | / | / |
| | Item 12 | / | 0.619*** | / | / |
| | Item 13 | / | 0.378*** | / | / |
| | Item 16 | / | 0.635*** | / | / |
| | Item 17 | / | 0.574*** | / | / |
| | Item 20 | / | 0.805*** | / | / |
| | Item 22 | / | 0.742*** | / | / |
| | **Factor 2 (perceptual aberrations/ hallucinations)** | 0.747*** | 0.557*** | / | / |
| | Item 1 | / | / | 0.812*** | / |
| | Item 7 | / | / | 0.835*** | / |
| | Item 19 | / | / | 0.910*** | / |
| | Item 23 | / | / | 0.875*** | / |
| | Item 24 | / | / | 0.834*** | / |
| | **Factor 3 (disorganization)** | 0.769*** | 0.638*** | 0.449*** | / |
| | Item 2 | / | / | / | 0.769*** |
| | Item 8 | / | / | / | 0.658*** |
| | Item 15 | / | / | / | 0.315*** |
| | Item 18 | / | / | / | 0.592*** |
| | Item 21 | / | / | / | 0.790*** |

Note. * p<.05, ** p<.01, ***p<.001

children and based on the participation of their parents. The scale was well received by parents, who were able to tell us how the investigated items allowed them to better understand their child's thoughts and actions.

The analysis of the scale identified three main factors, namely mistrust/paranoia, perceptual aberrations/hallucinations and disorganized symptoms. This finding is in line with the early psychotic symptoms reported in previous studies (Courvoisie et al., 2001; Craddock et al., 2018; Giannitelli et al., 2020). Moreover, it is consistent with the symptoms of the first criterion of diagnosis of schizophrenia (Two or

**Table 6**
Pearson correlation coefficients between the EPSy screening scale and the MASK, the reactive-proactive aggression questionnaire, the Conners scale and the DSM-V criteria.

| | | EPSy Current-Age total score (*r*) | Factor 1: mistrust/ paranoia (*r*) | Factor 2: perceptual aberrations/ hallucinations (*r*) | Factor 3: disorganization (*r*) | EPSy 2-YEARS total score (*r*) | Factor 1: mistrust/ paranoia (*r*) | Factor 2: perceptual aberrations/ hallucinations (*r*) | Factor 3: disorganization (*r*) |
|---|---|---|---|---|---|---|---|---|---|
| The reactive-proactive aggression questionnaire | PROACTIVE | 0.384*** | 0.328*** | 0.283*** | 0.292*** | 0,314*** | 0.310*** | 0.141* | 0.324*** |
| | REACTIVE | 0.517*** | 0.451*** | 0.437*** | 0.316*** | 0.408*** | 0.367*** | 0.315*** | 0.358*** |
| | TOTAL | 0.521*** | 0.451*** | 0.424*** | 0.341*** | 0.416*** | 0.384*** | 0.281*** | 0.384*** |
| MASK | Factor 1 | 0.711*** | 0.666*** | 0.451*** | 0.469*** | 0.568*** | 0.544*** | 0.350*** | 0.512*** |
| | Factor 2 | 0.634*** | 0.535*** | 0.622*** | 0.348*** | 0.635*** | 0.562*** | 0.577*** | 0.474*** |
| | TOTAL | 0.745*** | 0.671*** | 0.574*** | 0.460*** | 0.655*** | 0.606*** | 0.489*** | 0.545*** |
| DSM V | Hyperactivity | 0.379*** | 0.315*** | 0.206** | 0.383*** | 0.389*** | 0.355*** | 0.177** | 0.480*** |
| | Inattention | 0.318*** | 0.270*** | 0.148* | 0.328*** | 0.391*** | 0.362*** | 0.127* | 0.527*** |
| | Social Anxiety | 0.507*** | 0.571*** | 0.210** | 0.208** | 0.480*** | 0.578*** | 0.131* | 0.314*** |
| | Separation Anxiety | 0.495*** | 0.539*** | 0.311*** | 0.148* | 0.299*** | 0.338*** | 0.166** | 0.148* |
| Conners Scale | Behavioral difficulties | 0.658*** | 0.610*** | 0.510*** | 0.362*** | 0.571*** | 0.533*** | 0.438*** | 0.449*** |
| | Learning difficulties | 0.580*** | 0.571*** | 0.371*** | 0.312*** | 0.449*** | 0.471*** | 0.186* | 0.408*** |
| | Somatization | 0.323*** | 0.260*** | 0.394*** | 0.134* | 0.355*** | 0.299*** | 0.320*** | 0.310*** |
| | Impulsivity, hyperactivity | 0.434*** | 0.396*** | 0.343*** | 0.245*** | 0.536*** | 0.509*** | 0.294*** | 0.541*** |
| | Anxiety | 0.586*** | 0.641*** | 0.386*** | 0.149* | 0.540*** | 0.585*** | 0.320*** | 0.320*** |
| | Hyperactivity index | 0.608*** | 0.567*** | 0.450*** | 0.345*** | 0.614*** | 0.597*** | 0.334*** | 0.584*** |

Note. * p<.05, ** p<.01, ***p<.001

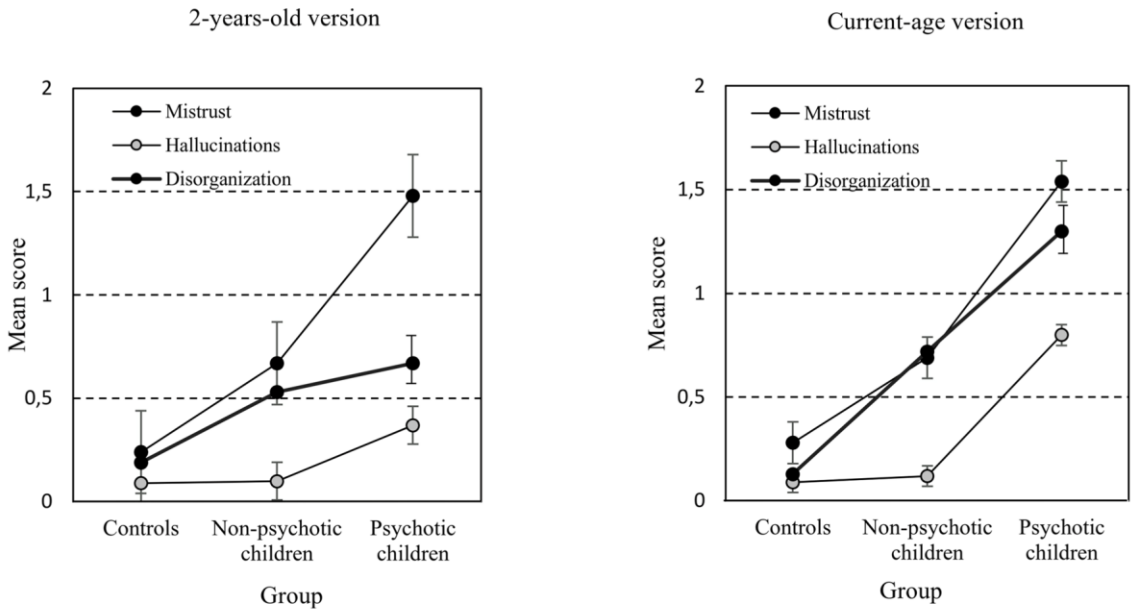


**Fig. 1.** Mean (1SEM) scores on the EPSy for each symptom and for each group as a function of the version of the scale.

more of the following symptoms are present for a significant portion of the time over a one-month period: Delusions, Hallucinations, Disorganized speech, Disorganized or catatonic behavior, Negative symptoms (American Psychiatric Association, 2013) and extends and complements what is already known about the COS (Kendhari et al., 2016), suggesting that the items included in the scale do indeed assess early psychotic symptoms from 2 years of age (Russell, 1994). The scale has good psychometric properties. Even if not perfect (RMSEA = 0.14), the results show a rather good adjustment between the two versions for the 3-factor model. Total scores as well as the scores for each factor (in both versions) are internally consistent and convergent validity is adequate when compared with other validated scales. Furthermore, good one-year test-retest reliability was observed for both versions. When using the scale for clinical purposes, we suggest using the 9th decile of the total score of each version, and to avoid using the cut-off of mean + 2SD because the data are not normally distributed. Finally, the scale sheds light on the presence from 2 years of symptoms that could be an earlier expression of current symptoms. Data also shows that, independently of the participant's age, the total score on the 2-years-old version predicts the total score on the current-age version, and this is also the case for each individual factor. To our knowledge, this is the first scale to permit such predictions.

The scale was also used to compare three groups of children, namely psychotic children, non-psychotic children and controls, to investigate possible differences in symptomatology and to observe any changes in this symptomatology between the age of 2 and the age at administration.

It is encouraging to see that the scores for each group differ for each factor and version, thus revealing specific profiles. Symptoms of mistrust are seemingly present in all three groups, both at the age of 2 years and at the present age, highlighting their presence at an early age. Furthermore, at the age of 2 years, they constitute the dominant symptoms. This means that, as already suggested in the literature (Preti et al., 2012; Wong et al., 2014), it may be difficult to differentiate these groups on the basis of mistrust. Nevertheless, although persecutory delusions and mistrust tend to be vague and difficult to distinguish from reality (Sikich, 2013), we observed a reliable distinction between the three groups in our study. Mistrust seems to be more prominent in psychotic children, less present in non-psychotic children and even less so in the controls (Schultze-Lutter et al., 2022; Zhou et al., 2018), both at the age of 2 years and at the present age.

As far as disorganization symptoms are concerned, they are seemingly less prominent than mistrust at the age of 2 years, but become as prominent as it at the current age of assessment. This cannot be due to the parents finding it difficult to retrospectively evaluate these symptoms at the age of 2, since there are already observable differences between the three groups at that age. Children classified as psychotic score as highly as those classified as non-psychotic, and both groups score higher than controls. Although disorganization is associated with the early onset schizophrenia (Nestsiarovich et al., 2017), it seems that at a very early age (2 years-old), this symptom therefore appears as an overall structural symptom of a neurodevelopmental disorder, as is the case in Attention Deficit Hyperactivity Disorder (ADHD) (Acosta, 2018; Magnus et al., 2023). At the same time, the disorganized symptoms seem to be more prominent in psychotic children at the current age and differ from the other two groups, as was observed in the study by Giannitelli et al. (2020). Despite this, non-psychotic children still scored higher than controls.

Hallucinations do not appear to be the dominant symptoms, and this is even more true at the age of 2 years. It should be remembered that hallucinations can be common in youth (Kelleher et al., 2012; Rubio et al., 2012; Sikich, 2013) and can be confused with normal behaviors, such as having an imaginary friend (McClellan, 2018). In contrast, psychotic children exhibited significantly more hallucinatory symptoms than control children and non-psychotic children in the current-age version, a finding which is consistent with previous studies (Craddock et al., 2018; Giannitelli et al., 2020; Jones et al., 2015; Kelleher et al., 2012; Kendhari et al., 2016).

Our study has some limitations that should be noted. First, as explained above, it can be difficult for parents to remember the behavior of their child at the age of 2 years, and all the more so if the child is significantly older at the time the current scale is completed. However, other assessments use the same methodology (Frigaux et al., 2019) and there is no correlation with the behavioral assessment at 2 years in any of them, irrespective of the number of years the parents need to think back. These data confirm that this methodology is effective. Secondly, another bias could be the tendency of parents to overestimate psychotic symptomatology at age 2, when it is present at the current age. However, in clinical practice, we realize that parents are not always aware of the symptomatology of their child at the current age, and tend to underestimate the current symptoms which would not go in the direction of this bias (Roy, 2008). Thirdly, the small sample size in Study 2 might be thought to compromise the reliability of the results of the group differences analysis (Cohen, 1977). However, this limitation should be considered in the light of the low prevalence of COS (0.04%) (Driver et al., 2013). Overall, this study can be considered as preliminary and it would be desirable to increase the sample sizes in order to obtain more precise results. Fourth, the Cronbach coefficient of the 3rd factor "Disorganization" being low, its consistency may be questioned. Indeed, the items that make up this subscale are very different, which means that it is not plainly unidimensional.

It is important to keep in mind that psychotic symptoms are not frozen in time and that they evolve. Screening at a specific time can thus represent a bias, since the diagnosis should be made over time (Marques Dos Santos et al., 2021). The fact of investigating in the EPSy the presence of symptoms at two distinct times (2 years and currently) therefore seems to respond both to the importance of early screening and to the need for a diagnosis which may change over time. To complete and consolidate the validity of screening for a diagnosis which may change over time, the need to carry out additional studies with scales such as the French version CAARMS (Krebs et al., 2014), the French version PQ-16 items (Lejuste et al., 2021) could be discussed (Fux et al., 2013; Loewy et al., 2005; Miller et al., 2003; Oliver et al., 2018).

To conclude, the EPSy screening scale is designed to help health professionals explore the complex characteristics of childhood early psychotic symptoms. This screening scale was designed for children aged 4 to 13 years and is of interest for two reasons: (i) it is of value for fundamental research in that it examines the evolution of psychotic symptoms in children as of the age of 2 years, and (ii) it is of clinical interest since it makes it possible to describe symptomatology both at age 2 and at the child's present age depending on the group to which the children are assigned (control children, psychotic children, non-psychotic children). One important point is that previous studies (Giannitelli et al., 2020) have described hallucinations as being the most significant symptoms in children and as being predictors of more severe disorders in adulthood. Our results suggest that the previous focus on hallucinations was perhaps somewhat misplaced. Symptoms of mistrust were found to be an important and very early indicator of psychosis, and symptoms of disorganization gain a similar status as mistrust as children grow older. They should therefore be taken into account for the intensive monitoring of children who could be qualified as being at ultra-high risk for developing psychotic symptoms (Schultze-Lutter et al., 2022).

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## CRediT authorship contribution statement

**Marie-Noëlle Babinet:** Conceptualization, Formal analysis, Investigation, Data curation, Methodology, Project administration, Writing – original draft, Writing – review & editing. **Caroline Demily:** Conceptualization, Methodology, Project administration, Writing – review & editing. **George A. Michael:** Conceptualization, Formal analysis, Methodology, Project administration, Writing – review & editing, Supervision.

## Declaration of Competing Interest

None.

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# CHAPITRE 2

## Le traitement du regard

# Les mécanismes généraux du traitement du regard

Conjointement au dépistage des symptômes psychotiques précoces de l'enfant, il semble important d'examiner les manifestations spécifiques telles que le traitement du regard qui peuvent être liées à la présence de ces symptômes. En effet, la présence de symptômes psychotiques peut être combinée à un traitement du regard atypique, entraînant des comportements oculaires spécifiques tels que des fixations prolongées sur des stimuli spécifiques, un évitement du contact visuel ou des mouvements oculaires désorganisés (Pinkham et al., 2003, 2011). De nombreuses études suggèrent que ces atypicités pourraient être liées à des difficultés à extraire les informations pertinentes de la région oculaire, y compris la direction du regard (Itier & Batty, 2009). Nous savons que les yeux et le regard jouent un rôle crucial dans l'interaction sociale chez tous les humains. En neuropsychologie expérimentale, et en neurosciences plus généralement, afin de pouvoir comprendre le fonctionnement pathologique, il est primordial de s'intéresser au fonctionnement typique.

Ainsi, afin de faire la lumière sur les données comportementales et les aspects qui ont trait à la détection et à la perception de la direction du regard, une revue narrative de littérature a été réalisée. Elle explore plusieurs modèles théoriques sur le traitement de l'information visuelle du regard afin de proposer une hypothèse unifiée. Des questions non encore explorées ont également été identifiées. Dans un second temps, les aspects neuronaux du traitement de l'information visuelle, tant au niveau sous-cortical que cortical, ont été examinés en mettant en exergue les étapes de traitement de l'information de bas et haut niveau. Enfin, les mécanismes de détection du regard ont été discutés via le prisme de divers troubles tels que par exemple la schizophrénie et la délétion 22q11.2.

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THEORETICAL REVIEW

# Eye Direction Detection and Perception as Premises of a Social Brain: A Narrative Review of Behavioral and Neural Data

Marie-Noëlle Babinet[1,2,3] · Manon Cublier[4] · Caroline Demily[1,3] · George A. Michael[2]

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**Abstract**
The eyes and the gaze are important stimuli for social interaction in humans. Impaired recognition of facial identity, facial emotions, and inference of the intentions of others may result from difficulties in extracting information relevant to the eye region, mainly the direction of gaze. Therefore, a review of these data is of interest. Behavioral data demonstrating the importance of the eye region and how humans respond to gaze direction are reviewed narratively, and several theoretical models on how visual information on gaze is processed are discussed to propose a unified hypothesis. Several issues that have not yet been investigated are identified. The authors tentatively suggest experiments that might help progress research in this area. The neural aspects are subsequently reviewed to best describe the low-level and higher-level visual information processing stages in the targeted subcortical and cortical areas. A specific neural network is proposed on the basis of the literature. Various gray areas, such as the temporality of the processing of visual information, the question of salience priority, and the coordination between the two hemispheres, remain unclear and require further investigations. Finally, disordered gaze direction detection mechanisms and their consequences on social cognition and behavior are discussed as key deficiencies in several conditions, such as autism spectrum disorder, 22q11.2 deletion, schizophrenia, and social anxiety disorder. This narrative review provides significant additional data showing that the detection and perception of someone's gaze is an essential part of the development of our social brain.

**Keywords** Eye direction detection and perception · Gaze · Social brain · Behavior and neural data

## Introduction

The face plays an essential role in human communication. It conveys information about other people's identity, gender, emotional states, and even personality traits (Bruce & Young, 1986; Emery, 2000; Hietanen, 2018; Kleinke, 1986). Within the structure of a face as a visual stimulus, the eyes are the first and most frequently fixated region, and gaze plays a central role in interindividual interactions (Kleinke, 1986). Indeed, the detection and perception of gaze provides valuable indications about other people's intentions, they allow us to identify whether we are the target of the gaze, and if not, to know who is being observed. While the functions of gaze have been the focus of social psychology research for a very long time (Kendon, 1967), studies of the cognitive processes and brain mechanisms associated with the detection and perception of gaze direction are more recent, although widespread in the field of cognitive neuroscience (Itier & Batty, 2009). These processes seem to take place automatically and effortlessly in individuals with typical development and are an indissociable aspect of social communication (Baron-Cohen, 1994). In contrast, in atypical conditions, such as social anxiety disorder, and in neurodevelopmental pathologies, such as autism and schizophrenia, these processes appear to be altered. This causes difficulties in social relationships that can

✉ Marie-Noëlle Babinet
marie-noelle.babinet@ch-le-vinatier.fr

1 Centre de Référence Maladies Rares à Expression Psychiatrique (GénoPsy), Centre Hospitalier Le Vinatier, 95 Boulevard Pinel, 69500 Bron, France

2 Unité de Recherche Étude des Mécanismes Cognitifs, Université Lumière Lyon 2, Université de Lyon, 5 avenue Pierre Mendes-France, 69676 Bron cedex, France

3 UMR 5229, CNRS & Université Claude Bernard Lyon 1, Université de Lyon, Institut des Sciences Cognitives Marc Jeannerod, 67 Boulevard Pinel, 69675 Bron Cedex, France

4 Unité d'hospitalisation, Pôle de psychiatrie de la personne âgée, Centre Hospitalier Le Vinatier, 95 Boulevard Pinel, 69500 Bron, France

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be reflected in the recognition of facial emotions and in the interpretation of other people's intentions.

Some researchers have advanced the hypothesis that eye contact acts as a communication intention detector. The hypothesis being that through its ability to induce an intention to communicate, eye contact directly activates channels of social cognition (Conty et al., 2007; Kampe et al., 2003; Schilbach et al., 2006; Wicker et al., 2003). This type of intention detector seems to be underpinned by specific subcortical and cortical mechanisms (Senju & Johnson, 2009b), making it a network of theory of mind and even social cognition. In light of the various investigations into detection and perception of gaze as premises of a social brain, this narrative review examines what behaviors can be observed, from birth to adulthood, in response to the direction of people's gaze. Then, we examine the related neural aspects. Once the typical functioning has been explicated, we focus on some atypical aspects. In an effort to synthesize the extant literature, new hypotheses are advanced relating to the cognitive and neural aspects of gaze direction detection and perception.

## Behavioral aspects of the detection and perception of gaze

It is well-established that infants are attracted to faces early in life, and research has tried to unravel the impact on newborns' attention and behavior of the detection and perception of gaze directed at them (direct gaze) or away from them (averted gaze). The earliest studies (Hood et al., 1998; Vecera & Johnson, 1995) already showed different behaviors in newborns in these two conditions, with a preferential orientation toward direct gaze. According to Itier and Batty (2009), preferential orientation for direct gaze can help to build a certain number of relational capacities and may constitute an early sign of the emergence of social interactions.

One subject of speculation and ongoing debate is why and how this preferential orientation toward direct gaze develops. From birth, newborns are able to catch another person's eye and to fix a direct gaze as long as their face is no further than 30 cm away (Bronson, 1974). It is highly likely that a fixation reflex exists from the first weeks of life, albeit unstable and short-lived due to low visual acuity (Allen et al., 1996). From birth and up to 9 months of life, stable, precise, and sustained fixation is obtained through foveal maturation. At the same time, increased sensitivity to contrast allows the infant to distinguish between and recognize static and dynamic shapes (Vital-Durand et al., 1996). During the first weeks and months of life, this sensitivity undergoes significant qualitative and quantitative changes (Bui Quoc, 2007). The 5-week-old newborn cannot perceive contrasts of less than 20%. From birth, however, the contrasts between the sclera, the pupil, and the iris of the eyes of others are easily perceived, even when the iris is clear, as long as the contrast in the eyes is greater than 20% (Vital-Durand et al., 1996). This suggests that the basic requirements for detecting the eyes are met quite soon after birth. In adults (between 24 and 28 years old in the studies of Burra, Baker, & George (2017); George et al. (2001); Kampe et al. (2001); Taylor, Itier, Allison, & Edmonds (2001)), the perception of the direction of the gaze tends to be more nuanced with behavioral responses to a direct gaze, which are faster than responses to an averted gaze. These behavioral responses also seem to be modulated by the orientation of the head, since the perception of gaze direction is more evident with a frontal view than with a 30°-deviated view (Coelho et al., 2006; Conty et al., 2007). It is assumed that the preferred orientation toward direct gaze serves to collect information about intentions, potential future interactions, or the focus of other people's attention. This information is important for social and nonverbal communication and tells one what to expect, what happens, and how to behave with peers (Itier & Batty, 2009).

Various interpretations have been proposed to account for newborns' preference for direct gaze. Baron-Cohen(1994) suggested the existence of the "Eye Direction Detector" (EDD), an innate module in the brain specifically dedicated to gaze processing. This module is part of a broader system called "The Mindreading System," the role of which is to determine the code and intentions of others and, therefore, to contribute to social interactions. According to Baron-Cohen(1994) and Brothers (1990), this system is supported by a specialized brain network called the social brain. The EDD has two functions: the first to detect the presence of eyes, and the second, to represent eye behavior. To explain the second function, Baron-Cohen's argument was based on what he called domain specificity, which is the idea that the eyes constitute a well-defined area with specific regions of contrast: a darker region (iris/pupil) and a white region (the sclera). Contrast sensitivity being a general property of the visual system (Baron-Cohen, 1994, 1995), the author suggested that after detecting the eyes, the EDD makes it possible to construct a representation of behavior, including a relationship between oneself and the person who is looking at us. He suggested that this enables the observer to imagine certain basic properties of intentionality. He also assumed that the EDD is activated once a face has been detected. Thus, the EDD is used to locate the relevant stimuli (i.e., the eyes) within a more global structured background (i.e., the face) and this should already be possible soon after birth. The direct gaze preference also can be explained using the two-process model proposed by Johnson et al. (Johnson, 2005; Johnson et al., 1991; Johnson et al., 2015; Morton & Johnson, 1991). The first process is a face-specific mechanism, named *Conspec*, set to detect faces of conspecifics. This mechanism is selectively tuned to the geometry of a face. The effectiveness and ubiquity of the simple T-shaped schematic face (i.e., the spatial

configuration of the two eyes, the nose and the mouth) suggest that face detection may be accomplished through a simple template-like process (Tsao & Livingstone, 2008). Computational models relying on algorithms detect and match basic features, which are much simpler than a whole face (rectangle features in the Viola Jones algorithm (Viola & Jones, 2004), qualitative contrast ratios between pairs of face regions (Sinha, 2002), and face parts (Ullman et al., 2002)). However, such algorithms carry out holistic detections, which means they necessarily detect the faces as spatially arranged sets of features. Indeed, such algorithms detect overlapping constellations of the basic features that constitute the entire face and, implicitly, enforce the overall layout of features. This process tuned to the geometry of a face (*Conspec*) is already present at birth (Morton & Johnson, 1991). The second process proposed by Johnson et al. (2015), is a domain-relevant mechanism, named *Conlearn*, that progressively specializes in face recognition from the age of two months by acquiring and retaining specific information about the visual characteristics of conspecifics. Direct gaze detection preference is probably supported by the detection of faces at birth due to the domain-specific*Conspec* mechanism (Morton & Johnson, 1991). There are seemingly at least two overlapping ideas in the two models laid out above. The first concerns the existence of specific mechanisms that are already present and operational at birth, that continue to mature after birth and support the subsequent development of higher-order, learning-based mechanisms of great importance for social cognition and interactions. The difference is that the first model is more eye-specific, whilst the second is more face-specific. The second overlapping idea is not as direct as the first. It supposes a specific time-course of information processing in which core face-like stimuli are detected before eye-like stimuli. This aspect is important since it describes how certain stimuli are given processing priority and how they are ranked for further processing.

The existence of a mechanism specifically devoted to detecting faces in the environment (and hence, the eyes) has been questioned by an alternative view according to which faces are preferred because they are a collection of perceptual structures, the properties of which attract newborns' attention. According to this view, attentional biases toward these structural properties present in faces lead to the newborns' preferences, yet the attentional biases are not specifically built for detecting faces and therefore eyes. They probably derive from the functional properties of the immature newborns' visual systems and are useful for both faces and non-face stimuli. Such structural properties appear relevant because they allow newborns to successfully detect and identify faces, i.e structured wholes, when embedded among other non-face stimuli (Simion et al., 2001). This view is consistent with the notion the newborns' immature visual system is sensitive, not only to a certain range of spatial frequencies, as described by the contrast sensitivity function (see Acerra et al., 2002), but also to other higher-level structural properties, as demonstrated by newborns' preference for horizontal versus vertical stripes (Farroni et al., 2000). In adults (mean age 20 years old in the study by Olk et al. (2008)), gaze direction judgments are possibly based on the outcome of competition between different gaze direction signals such as luminance cues and geometric cues. In addition, faces are three-dimensional objects that move and, importantly, manifest visual traits that are present simultaneously. These characteristics render faces probably the most interesting stimulus experienced by newborns in their immediate environment, all the more so because they are the most frequent stimulus that appears within a distance of 30 cm (Bui Quoc, 2007). Indeed, a study conducted on newborns between 13 and 168 hours old by Farroni et al. (2005) hypothesized that if up-down asymmetry is crucial to determining face preference, then the contrast polarity of the elements should not interfere (i.e., face-sensitive view, see Johnson et al., 2015, for a discussion). The authors found that the contrast polarity of the stimulus is a determinant of this preference for faces. From the age of 4 months, infants seem sensitive to the contrast polarity that results from the typical perceptual pattern of the eyes, i.e., the black pupil on a white sclera (Michel et al., 2017). Similarly, adult observers are highly inaccurate in judging gaze direction from pictures of human eyes with negative contrast polarity (regardless of whether the surrounding face is positive or negative), even when the negative pictures of eyes have the same geometric properties as positive images that have been judged accurately (Ricciardelli et al., 2000). In another study involving a visual research task, when the contrast polarity intrinsic to the eye (i.e. a conspicuous (white or colored lighter than the iris color) or inconspicuous (colored the same or darker than the iris color) sclera) was varied adults detected gaze (direct or averted) more accurately and rapidly with conspicuous sclera (Yorzinski & Miller, 2020). Furthermore, this perceptual and sensory hypothesis is backed by the fact that the eye itself, as a visual stimulus, has a number of simple and powerful characteristics such as relatively high contrast and shape, making it particularly simple to detect (Langton et al., 2000). Other features may also need to be coded, such as angle of the head or body, but the information within the eye region is clearly important (for a review see Clifford & Palmer, 2018). The eye may be a special stimulus only in the sense that a vast amount of sensory information can be recovered from it using simple processing mechanisms, such as interactions between specialized cells in the visual system (Langton et al., 2000). From an evolutionary point of view, the extraction of properties of the eye region can lead to a gradual construction of a representation, thus shaping their social development, and eventually resulting in adult adaptive specializations (Farroni et al., 2003).

Whilst attentional priority is given to the person who is staring at us, the emotional responses this elicits are varied (Kendon, 1967). Eye contact through mutual direct gaze gives the impression of being stared at and triggers physiological arousal (Hood et al., 2003; Kampe et al., 2001; Kawashima et al., 1999; Senju & Johnson, 2009b). Early research found a greater electrodermal response when participants looked at the eyes when examining pictures of faces compared with when they looked at the mouth area (McBride et al., 1965), and direct gaze elicited a stronger electrodermal response than averted gaze (Nichols & Champness, 1971). These results were confirmed by Hietanen et al. (2008), who also showed that arousal was greater when eye contact was established between the participant and another person as opposed to contact between the participant and a photograph. Similar results were found when electrocortical activity was used as a measure of arousal (Hietanen et al., 2008; Kampe et al., 2003). Direct gaze therefore not only attracts attention and gains processing priority, but also increases physiological activity testifying to an emotional response, probably related to approach/avoidance responses (Adams & Kleck, 2003, 2005). The notion of approach and avoidance supports the idea that the capacity to process gaze information plays a role in behavioral intentions, defined by Baron-Cohen(1995) as "primitive mental states insofar as these are the basic states that are necessary to be able to understand the universal movements of all animals: approach and avoidance" (pp. 33-34).

In conclusion, preferential orientation toward direct gaze seems to be present soon after birth and to prime autonomous physiological activity. Furthermore, it seems to depend (i) on the presence of a specific facial configuration that maintains the spatial relationships between the components of the face (Farroni et al., 2002; Farroni et al., 2006, 2007; Morton & Johnson, 1991) and is used to identify the direction of gaze (Baron-Cohen, 1994), and/or(ii) on a collection of visual perceptual properties (Batki et al., 2000; Langton et al., 2000; Simion & Giorgio, 2015). In our opinion, these three theories (Baron-Cohen, 1994; Morton & Johnson, 1991; Simion & Giorgio, 2015) are not necessarily mutually exclusive. Indeed, they may be integrated in a more general framework. For instance, eye detection and perception may include a pictorial encoding step extracting details of the lighting, grain and salient areas of high contrasts in the face. This captures the static pose and expression seen on a face (Bruce & Young, 1986). It may be hypothesized that a contrast processing step specific to the "eye" stimulus extracts specific perceptual information from the eye region (dark/white contrasts) and determine the salience of the eye region based on the percentage of contrast. In a very recent study, Riechelmann et al. (2021) asked the question of the origin of gaze effects following their results highlighting the averted-gaze advantage. They consider that the increase in the salience of the white of the eye (i.e., sclera) for averted gaze (compared with direct gaze) is at the origin of the observed effects. We make the hypothesis that a direct gaze is associated with more contrast than an averted gaze. Contrast is the intrinsic property of an image, which quantifies the difference in brightness between the light (e.g., sclera) and dark (e.g., pupil) parts of the image (here, the eye). This difference in brightness, and therefore the contrast, is different for a direct gaze (sclera/pupil/sclera) than for an averted gaze (sclera/pupil or pupil/sclera), because contrast is not only determined by the presence of dark and light areas, but above all by their spatial arrangement and configuration. For instance, the eye stimuli presented in Fig. 1 show a significant difference in contrast between direct gaze and averted gaze. Areas of greater contrast (generally associated with direct gaze) would receive higher processing priority and help provide a faster, preferential response, such as orientation towards that area and a subsequent increase in physiological arousal.

In our opinion, there are still two gray areas and studying these would provide answers to these questions. First, we believe that the order in which stimuli are processed (face first or eyes first) is the fundamental difference between the aforementioned theories and that to our knowledge, this has not yet been fully investigated. Indeed, Langton (2000) and Ricciardelli and Driver (2008) studied these effects, but concomitantly with the impact of the orientation of the head. In their studies, they have shown that gaze perception is not only determined by the eye region but also by some parts of the face. Moreover, this perception seems to depend on the time constraints for judgments of direction of gaze. Furthermore, it is surprising that there is no mention in the relevant literature of a third possibility, i.e., synchronous and parallel processing of the eyes and the face. Indeed, the processing of the eyes could occur in parallel and in complementarity to the processing of the more general features of the face. Studying this question could shed light on the time course of information processing during the detection of gaze direction and, consequently, on which theory is closest to reality. There are several ways to assess the which-comes-first question. For instance, one experiment could involve adult participants who would be presented with the sketch of a face and required to make an eye-direction judgment (i.e., the eyes look at me vs. they look away) as quickly as possible. A temporal asynchrony could be introduced between the presentation of the face (without the eyes) and the presentation of the eyes in such a way that the whole face would appear in a face-eyes order, or in an eyes-face order. During very short time intervals, asynchrony is not consciously perceived. By recording response times, this would allow an assessment of whether preferential processing of direct gaze (as compared to averted gaze) is most visible when the face comes first, or when the eyes come first. This would answer the order of processing question.

Second, the models described so far try to explain how we perceive a specific area of the face (i.e., the eyes) characterized


**Fig. 1** Direct gaze and averted gaze. Two stylized stimuli representing direct gaze (**a**) and averted gaze (**b**). The cartoon probably does not correspond to real-world eyes. However, there is such variability in actual characteristics in human eyes (depending on age, gender, ethnicity, weight, individual characteristics…) that it is extremely difficult to fabricate a single type of stimuli that represents them. Five, successive, luminance measurements were taken using a Minolta LS-110 photometer. The contrast for the averted gaze is equal to 59.9% (averted gaze luminance for the sclera (white) = 136.31 (±4.95) cd / $m^2$; averted gaze luminance for the pupil (black) = 34.19 (±7.70) cd / $m^2$) and the contrast for the direct gaze is equal to 65.67% (direct gaze luminance for the sclera (white) = 104.1 (±5.43) cd / $m^2$; direct gaze luminance for pupil (black) = 21.57 (±8.75) cd / $m^2$). There is indeed a difference in contrast with a stronger contrast (6% more) for direct gaze. Differences of this order may be sufficient to change the speed of processing of visual information

by high contrast, defined by a darker region (iris/pupil) and a white region (the sclera). It is thus supposed that such salient perceptual features are given processing priority, and this is what defines preferential orienting. This hypothesis could be assessed by parametrically varying the contrast between the face and eyes, but also within the eye in a gaze direction judgment task. If the saliency hypothesis is correct, then faster responses for direct gaze (compared with averted gaze) are to be expected with increasing eyes/face contrast, with increasing iris/pupil contrast, and the fastest responses would be expected when increased iris/pupil contrast is combined with decreased eye/face contrast (this is the situation where gaze direction should stand out).

## Neural aspects of the detection and perception of gaze

### Low-level visual information processing

For 30 years, evidence obtained from behavioral, neuroimaging and electrophysiological studies has supported the hypothesis of specialized neural networks involved in eye and gaze processing (Haxby et al., 2002; Itier & Batty, 2009; Nummenmaa & Calder, 2009; Wicker et al., 1998), starting at retina level. As previously mentioned, foveal development associated with increased sensitivity to contrast plays an important role (Johnson, 2003) in processing high-contrast areas and in sustaining fixation. This seems to support the idea of the subsequent development of specialized cortical zones for the processing of the eyes and, more generally, the face. The course of visual information processing thus provides clues as to how retinal information translates into relevant information that biases attention (Bisley, 2011). Fibers from the retina travel along the optic nerve and axons either (i) reach the lateral geniculate nucleus (LGN) and then the primary visual cortex (or striate cortex), constituting the geniculostriate pathway (Ling et al., 2015; McAlonan et al., 2008); (ii) or first reach the superior colliculus, the pulvinar of the thalamus and the amygdala before reaching the extrastriate parietal and temporal areas, constituting the extrageniculate pathway (Knudsen, 2011; Robinson & McClurkin, 1989). It is thought that these two pathways operate simultaneously and in parallel, although it has been hypothesized that the extrageniculate pathway offers faster signal transmission (Mizzi & Michael, 2016). Both pathways are thought to play a role in eye and gaze processing, which needs to be more precisely defined in order to understand how information processing progresses from low to higher-levels and contributes to social interactions.

Within the geniculostriate pathway, inputs to the LGN include both the first synapses from the retinal ganglion cells, as well as massive feedback from the primary visual cortex and the thalamic reticular nucleus that greatly outnumber the retinal inputs (Sherman & Koch, 1986). This makes the LGN an opportune control structure to modulate the transmission of visual information. At the end of the geniculostriate pathway, single cells in the primary visual cortex respond vigorously to the whole eye as a stimulus (Langton et al., 2000). These cells respond in three spatially defined parts of the eye: the two visible parts of the sclera and the pupil. This enables the primary visual cortex to respond to gaze direction. When gaze direction changes the pupil shifts, causing a change in contrast. In addition, as the direction of gaze changes, the response of the cells sensitive to the scleral parts also changes. Neurons in the primary visual cortex represent luminance changes by dynamically adjusting their responses when the luminance distribution changes (Wang & Wang, 2016). This results in the detection of changes in gaze direction (Langton et al., 2000).

Within the extrageniculate pathway, the physiological properties of cells in the superior colliculus, the pulvinar and the amygdala may also contribute to emitting elementary signals of importance in terms of the direction of other people's gaze (Grosbras et al., 2005; Hoehl et al., 2009; Itier & Batty, 2009). The superior colliculus is involved in integrating spatial information and conveys topographic information on the face (Van Le et al., 2020). For instance, neurophysiological

evidence in monkeys suggests that neurons in the superior colliculus respond more strongly to face-like stimuli (Van Le et al., 2019). Furthermore, they are sensitive to the saliency of stimuli (Shen et al., 2011; Shen & Pare, 2014), making the involvement of the superior colliculus in both the detection of faces and the selection of salient features in faces for saccadic eye movements a plausible theory (Horwitz & Newsome, 2001).

In turn, the pulvinar incorporates important aspects of visual salience (Robinson & Petersen, 1992), probably by detecting regions or patterns of interest (Michael et al., 2016; Michael & Desmedt, 2004) and prioritizing them for processing (Michael & Gálvez-García, 2011). Importantly, primate pulvinar cells respond clearly and consistently to stimuli moving in all directions, providing the visual system with information about the location of a movement, although there are signs of orientation selectivity (Petersen et al., 1985). Recent neuroimaging evidence has shown that the pulvinar conveys information on faces that is nonselective in terms of spatial frequency or emotional expressions (McFadyen et al., 2017). Finally, there is mounting evidence that the pulvinar plays an important role in attention (Petersen et al., 1987) and that damage to this nucleus can contribute to attention deficits (Danziger et al., 2002; Michael et al., 2001; Michael & Buron, 2005). So far, we can assume that the superior colliculus and the pulvinar contribute to the detection of gaze direction at least through the coarse processing of face-like stimuli, the analysis of salient regions of contrast (e.g., the regions of the eyes), and the efficient detection of movement (i.e., an approaching face or gaze that changes direction). On this last point, it is also interesting to note that neurophysiological investigations have uncovered a disynaptic pathway that transfers motion signals through the superior colliculus and the pulvinar from the retina toward the extrastriate cortical areas specialized in motion processing (Lyon et al., 2010). Interestingly, recent psychophysical evidence suggests that this pathway guides attention to moving stimuli without awareness (Mizzi & Michael, 2018), which might be the means by which the extrageniculate pathway prioritizes the processing of changes in gaze direction.

It has been known for several decades that the amygdala participates in emotional processes (Aggleton & Young, 1999) and responds to emotional facial expressions (Sato et al., 2004). Its role in this type of social information processing is well established. Whether and how it may be involved in gaze direction processing, however, is not easy to apprehend. The amygdala contains neurons that respond both selectively to stimuli from unique sensory modalities (visual, tactile, auditory, etc.) and to integrated multisensory stimuli (Morrow et al., 2019), suggesting that the amygdala may bind together elementary signals carried by facial expressions, voices etc. Recent investigations in humans have shown that neural responses in the amygdala increase in response to facial stimuli, independently of spatial frequency or emotional expressions (McFadyen et al., 2017). Furthermore, there is evidence that the right amygdala exhibits an increased response to direct gaze (Kawashima et al., 1999; Senju & Johnson, 2009b). Thus, the amygdala is thought to be involved in the bottom-up processing of faces and the eye region through connections with the pulvinar (Itier & Batty, 2009;Vuilleumier et al., 2003 ; Vuilleumier & Schwartz, 2001), forming a rapid pathway for the transfer of generalized information about faces (McFadyen et al., 2017). One interesting recent hypothesis is that more precise information on face structure giving rise to the perception of facial expressions is transferred to the amygdala via a slower route that involves the primary visual cortex and conveys high spatial frequencies (McFadyen et al., 2017). This tallies well with the fact that amygdala responses to facial expressions are predominantly driven by judgments about the eye region (Wang et al., 2014). These findings suggest that the amygdala constitute one of the convergence points of information on faces and gaze obtained from forward projections from the superior colliculus and the pulvinar, and from backward projections from the primary visual cortex after direct input from the LGN.

Overall, the properties of the structures that form both the geniculostriate and the extrageniculate pathways suggest that the low-level processing within these pathways provides sufficient information to detect static and approaching faces, localize the contrasts that designate the eye region, detect a direct gaze, spot changes in the direction of gaze, and confer attentional priority on the relevant aspects of the stimuli without conscious awareness. Combined with the fact that at birth these pathways are sufficiently developed to take on these processes, these observations concur with theories on the elementary and automatic mechanisms that convey information about, and contribute to, the detection of the direction of gaze (Baron-Cohen, 1994; Morton & Johnson, 1991; Simion & Giorgio, 2015), and which form a basis for social interaction through the processing of emotional information conveyed through facial expressions (Vuilleumier et al., 2003; Vuilleumier & Schwartz, 2001). Furthermore, the amygdala is involved in priming approach/avoidance responses (Davis & Whalen, 2001), which can induce autonomous physiological reactions when a direct gaze is detected (Hietanen et al., 2008).

Several authors have suggested that the geniculostriate and the extrageniculate pathways interact to detect gaze and faces. These pathways may provide a representation of contrast distribution, information which would then be transmitted to the striate cortex (Acerra et al., 2002; Farroni et al., 2004, 2013; Nakano & Nakatani, 2014). Senju and Johnson (2009a, 2009b) suggested the possibility of an accelerated modulator associated with the effect of eye contact. The effect of eye contact would appear to be mediated by the extrageniculate pathway (de Gelder et al., 2003; Johnson, 2005; Morton &

Johnson, 1991) because of its assumed higher information transmission speed and the nature and complexity of the information it conveys. This could modulate activity of the geniculostriate pathway (McFadyen et al., 2017) and beyond (Johnson, 2005). The organization in a dual parallel extrageniculate and geniculostriate system led Senju and Johnson (2009a, 2009b) to suggest a direct gaze detector system might exist. The extrageniculate pathway would detect social interaction intent, through detection of direct gaze for instance. This information would then be transmitted and combined with that gathered by the geniculostriate pathway, eventually leading to the conscious perception of being stared at. Higher-level processing in other cortical areas would provide a subsequent more detailed analysis of the situation to promote social interaction and situational behavior.

## Higher-level visual information processing

The story therefore does not end with the mere convergence of information from two separate pathways in the amygdala. Cortical areas involved in higher-level visual information processing seem to contribute to detecting the direction of gaze. Integrated information from the geniculostriate and extrageniculate pathways converges towards extrastriate cortical areas (Prasad & Galetta, 2011) and then reaches certain portions of the fusiform gyrus (FG) and the superior temporal sulcus (STS)(Seltzer & Pandya, 1978). This suggests that the input into these cortical areas contains all aspects of the information already handled during the low-level stages of processing and that, consequently, some involvement in gaze detection and perception is to be expected (Grosbras et al., 2005). This idea is supported by the observation that the detection of direct gaze increases functional connectivity between the amygdala and the FG (George et al., 2001). Furthermore, the FG exhibits an increased response to direct gaze, mostly in the right cerebral hemisphere (Senju & Johnson, 2009b). Interestingly, it is the medial part of the posterior FG (FGm) that receives input from the striate and extrastriate cortices (Zhang et al., 2016). Like the majority of neurons in the amygdala (Morrow et al., 2019), neurons in the FGm are multisensory, suggesting that the FGm may bind together signals carried by facial expressions and voices for the purposes of social communication (Zhang et al., 2016). The perception and identification of faces (Iidaka, 2014) as well as the analysis of gaze provide visual clues during social communication.

As for the STS, it would seem to be a structure of higher cognitive integration and the wealth of afferences to and efferences from the STS gives credit to this hypothesis (Desimone & Ungerleider, 1986; Seltzer & Pandya, 1989a, 1989b, 1994; Specht & Wigglesworth, 2018). Some authors have suggested that the STS can be divided into five areas along an antero-posterior pathway, each area supporting a function: theory of mind, biological motion, faces, voices, language (Beauchamp, 2015). The posterior segment of the STS (pSTS) also is thought to be a key area for dynamic facial processing and code changes in expression and gaze (Cheng et al., 2018; Iidaka, 2014). Furthermore, this tallies well with earlier work showing that different head views are associated with distinct responses in the pSTS (Fang et al., 2007; Natu et al., 2010). The anterior part of STS (aSTS) seems to feature a fine-grained representation of specific gaze directions (Calder et al., 2007; Carlin et al., 2011; Carlin et al., 2012) since it exhibits graduated activations in response to the direction of gaze. This specificity of the aSTS is supported by the fact the responses are independent of other factors such as head orientation or head view (Calder et al., 2007; Carlin et al., 2011). These studies therefore suggest the existence of view invariant processes in gaze direction subtended by the aSTS (Carlin & Calder, 2013). Of particular interest in the present paper, in order to better understand the complete path of neuronal information concerning gaze detection and perception, is the fact that the STS receives afferents from the striate (Montero, 1980) and the extrastriate cortices, as well as from the FG (Seltzer & Pandya, 1978). A further characteristic of the STS is that it shows anatomical asymmetry between the left and right cerebral hemispheres. It is longer on the left, but deeper on the right (Leroy et al., 2015). This asymmetry is genetically coded since it would appear to develop *in utero*(Kasprian et al., 2011). A neural population responding specifically to the direction of gaze is hosted in the right STS (von dem Hagen et al., 2014). This has been confirmed by studies using Transcranial Magnetic Stimulation (TMS) techniques and shows that transient inhibition of the right posterior STS disturbs orientation towards the eyes and, therefore, indirectly the perception of gaze (Saitovitch et al., 2016). In turn, the left STS exhibits increased activity during the passive viewing of averted gaze (Hoffman & Haxby, 2000). Therefore, both cerebral hemispheres appear to participate in the detection of gaze direction, but in a different way depending on where the gaze is directed. In conclusion, the STS seems to play a role in representing a person's gaze direction (Carlin & Calder, 2013; Hoffman & Haxby, 2000; Perrett et al., 1985; Perrett et al., 1990; Senju & Johnson, 2009b) with a progressive anterio-posterior representation. Neurons in the pSTS may represent the detection of gaze direction changes depending on head movement whilst neurons in the aSTS might be specifically dedicated to the more view invariant aspects of the direction of gaze (Calder et al., 2007; Carlin & Calder, 2013). This information would then be transmitted to the anterior cortical regions to enable joint attention.

Several other areas appear to be involved in gaze direction detection and perception, such as the intraparietal sulcus (IPS) and the temporoparietal junction (TPJ)(Senju & Johnson, 2009b; von dem Hagen et al., 2014). It is less clear, however, whether these structures are directly involved in determining gaze direction or whether they are recruited subsequently to

reorient attention toward the other person's gaze (i.e., joint attention; Carlin & Calder, 2013; Hoffman & Haxby, 2000; Itier & Batty, 2009). The literature notably suggests that the IPS plays a role in the endogenous orientation of spatial attention and that the TPJ could act as a circuit breaker by interrupting ongoing activities to reallocate available attentional resources to salient stimuli (Corbetta et al., 2008; Corbetta & Shulman, 2002). As far as gaze direction detection and perception are concerned, direct extrageniculate input may activate the IPS in order to reorient attention to socially relevant stimuli (e.g., when someone is staring at us). This might be facilitated by the activation of the TPJ, which, in this case, would act as a circuit breaker (Grosbras et al., 2005). Finally, activity in the frontal cortical areas has also been reported to occur in response to direct gaze (von dem Hagen et al., 2014), especially in the right hemisphere (Senju & Johnson, 2009b). Again, these results are inconsistent and these structures might be indirectly involved in coding emotional information conveyed through gaze, or in promoting joint attention (Carlin & Calder, 2013; George et al., 2001; Itier & Batty, 2009).

Overall, these findings make it possible to outline a dynamic cortical network dedicated to higher-level information processing. The core role of this network being to detect gaze direction on a static or moving head, and decode the dynamic microstructural changes on the face that form emotional facial expressions. This network also encompasses structures devoted to controlling and reorienting attention toward relevant social cues and promoting joint attention (Mosconi et al., 2005). Finally, the right cerebral hemisphere seems to be more specifically involved in the detection of direct gaze (Grosbras et al., 2005).

## Awareness of direct gaze

All the aforementioned structures seem to be engaged differently or in qualitatively different processing depending on whether or not there is conscious awareness of direct gaze (Madipakkam et al., 2015). Indeed, in situations where exposure to face is being masked, and thus participants are unaware of perceiving faces, the FG, the STS and the IPS still respond to the direction of gaze, but their responses are weaker than for visible faces. Furthermore, direct gaze elicited greater responses than averted gaze when participants were aware of the faces, but smaller responses when they unaware (Madipakkam et al., 2015; for review: Sterzer et al., 2014). These data suggest that even when there is no awareness of being stared at, certain structures in the gaze detection network still generate a neural response. Social information about being the focus of someone's attention can thus be processed nonconsciously, a kind of blindsight (Kim & Blake, 2005; Leopold et al., 2002; Sterzer et al., 2014; Tong et al., 2006). One interesting finding is that the extrageniculate pathway is also involved in the nonconscious processing of emotional stimuli (Liddell et al., 2005; Morris et al., 1999; Troiani & Schultz, 2013). The study by Madipakkam et al. (2015) did not report any activity in the superior colliculus or the pulvinar. This may be due to the neural signals in these structures being too weak to show up in the results. It therefore is interesting to ask the question as to whether amygdala responses when participants were unaware of the stimuli were due to input from these extrageniculate structures or to back-projections from cortical areas. The involvement of the extrageniculate pathway in the nonconscious feeling of being stared at is therefore an avenue for further investigation.

Overall, the neural processing of gaze seems to involve different networks. In the light of all the data reviewed, this paper proposes to describe how information processing builds through specialized networks, to provide the most complete explanation possible of the neural processing of gaze. Although further research is needed, it would appear that detecting gaze and its direction is supported by a specialized system (Fig. 2) combining (i) whole low-level processing pathways, namely the extrageniculate pathway (i.e., superior colliculus, pulvinar and amygdala; Kawashima et al., 1999; Senju & Johnson, 2009a, 2009b) and sections of the geniculostriate pathway (i.e., the primary visual cortex), (ii) and temporal structures, including the FG which ensures multisensory processing (George et al., 2001; Grosbras et al., 2005) and the STS, which enables the representation of a person's gaze direction (George et al., 2001; Grosbras et al., 2005; Hoffman & Haxby, 2000; Itier & Batty, 2009; Perrett et al., 1990). It would appear that luminance contrast derived from spatial and topographical aspects of the face triggers activity within the striate cortex related to the direction of gaze. This activity is thought to contribute toward building a representation of the direction of gaze within the pSTS containing retinotopic information and, thus, enable the subsequent construction of a dynamic representation of gaze direction and movements. This information may also enable the construction of a view-invariant representation within the aSTS (Carlin & Calder, 2013; Cheng et al., 2018). Other cortical structures seem to be involved, but their role is less clear. These are (iii) parietal areas, such as the IPS and the TPJ, that may help to allocate attentional resources (Carlin & Calder, 2013; George et al., 2001; Grosbras et al., 2005; von dem Hagen et al., 2014) and (iv) frontal areas that might be involved in coding emotional information conveyed by a person's gaze, or promoting joint attention (Carlin & Calder, 2013; Itier & Batty, 2009). Finally, the right cerebral hemisphere seems to be more involved in the processing of faces with direct gaze (George et al., 2001; Senju & Johnson, 2009b), while the left hemisphere may signal the presence of a face looking somewhere else (von dem Hagen et al., 2014).

While the literature contains some information about the potential role of each hemisphere in gaze perception, very few

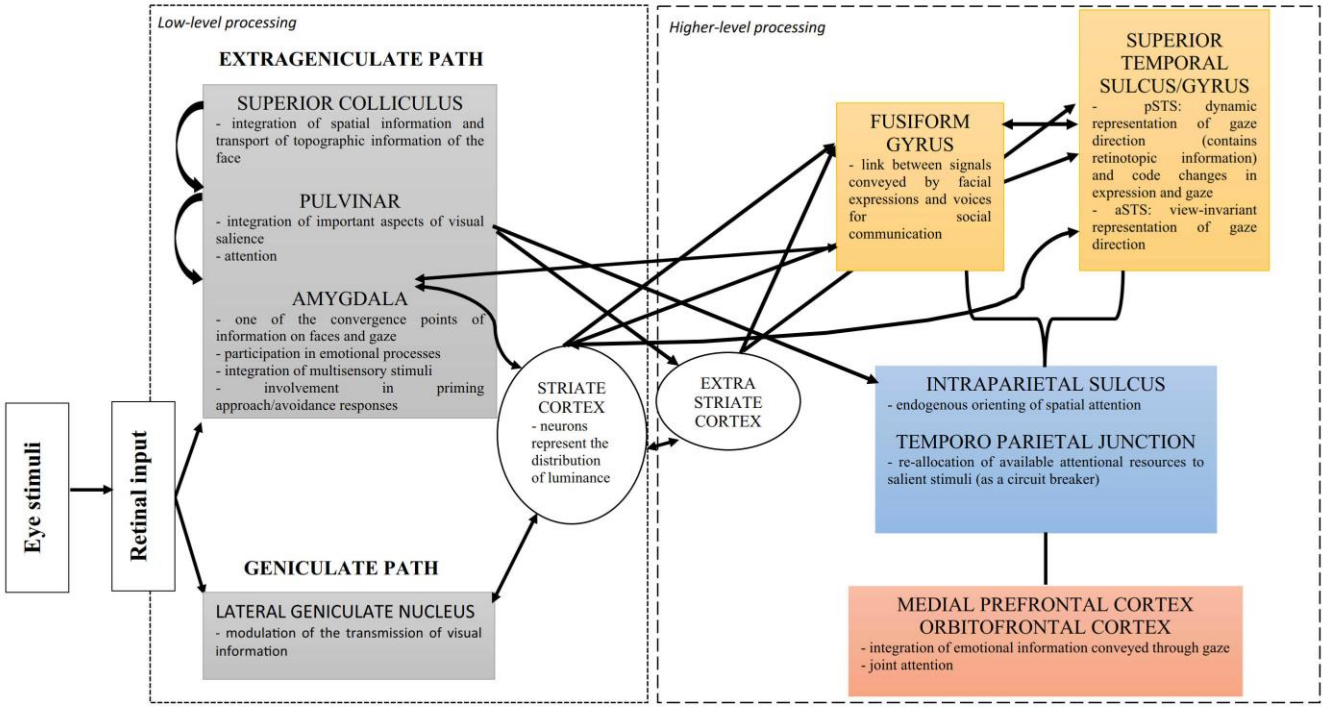


**Fig. 2** Gaze detection model

studies have investigated the possibility of any putative hemispheric asymmetry. A visual field effect on perception of gaze direction has been found (Ricciardelli et al., 2002). In that study, participants with typical development viewed eye stimuli displayed on a computer monitor and were required to judge the direction of gaze. A Left Visual Field advantage was found (more correct answers), indicating right hemispheric dominance. This hemispheric dominance seems specific to the perception of gaze direction and is already present at the age of 4-6 months (de Heering & Rossion, 2015). However, despite this right hemispheric dominance, both hemispheres seem to be involved in the detection and perception of gaze direction, as previously mentioned (George et al., 2001; Senju & Johnson, 2009b; von dem Hagen et al., 2014), meaning that they have to interact in some way at some time. This last point is not clear, and further investigation is needed. Determining the exact direction of gaze and who is the focus of someone's attention may result from coordination between the two hemispheres through interhemispheric connections, in the posterior sections of the corpus callosum, for example. According to Hellige (1993) and Kinsbourne (1970, 1982, 2003), the two hemispheres mutual inhibit each other through callosal connections, resulting in a functional equilibrium. The activation of one hemisphere during a specific process would inhibit the other hemisphere in order to reduce interference (Kinsbourne, 1975), but in a way that also allows the level of asymmetric activations to be coordinated and regulated (Banich & Karol, 1992). It is possible that right hemisphere processes relating to direct gaze detection are rendered more efficient through the inhibition of left hemisphere averted gaze detection processes. To assess the hypothesis of hemispheric interaction and coordination in gaze detection and perception, a cueing paradigm could be used in which the cues would be chimeric facial stimuli. For example, participants could be required to fixate a central fixation sign and quickly detect a dot target presented on a computer monitor. The target could be preceded by a tachistoscopically presented chimera composed of a half-face with direct gaze and another half-face with averted gaze. The midline of the chimeric face would coincide with the fixation sign so that each half-face would be preferentially projected to each hemisphere. The target dot would be placed either at the location of the directed gaze or the averted gaze. Overall responses would be expected to be faster for targets appearing at the location of direct gaze (compared with averted gaze). If the hemispheric asymmetry hypothesis is correct, i.e., direct gaze is preferentially processed by the right hemisphere and averted gaze by the left hemisphere, then faster responses are to be expected for targets appearing in the left visual hemifield where a direct gaze is presented, and for targets appearing in the right visual hemifield where an averted gaze is presented compared with the opposite hemifield-gaze direction combinations. However, this paradigm also would provide information on whether the detection of direct gaze is achieved through inhibition exerted by the right hemisphere on the left hemisphere. Indeed, if the right hemisphere is stimulated through a direct gaze (appearing in the left hemifield) but the dot-target is in the left hemisphere (right hemifield), then responses would be much slower than the opposite combination, even if slower responses are expected in both scenarios due to the attraction

of attention toward direct gaze and away from the dot target. Similar paradigms would provide interesting information on hemispheric processes.

## Disturbance of gaze perception and its impact on social cognition and socially adaptive behavior

The detection of the direction of gaze is a useful signal since it directly provides information on the person's interest and the presence of possible dangers nearby (Emery, 2000). What one looks at also provides clues to the person's inner state, such as what they know and what they want (Emery, 2000; Kendon, 1967). Given the importance of gaze direction detection and perception for social interaction, it is expected that any disturbance of the ability to detect or even follow another person's gaze is likely to impair social cognition and behavior, and could also lead to the misinterpretation of intentions and mental states (Cañadas & Lupiáñez, 2012). Several disorders are associated with abnormal gaze perception and eye contact. Here, we will discuss autism spectrum disorder, schizophrenia, social anxiety disorder, and finally 22q11.2 deletion syndrome. This selection is based on the fact that these are disorders associated with impaired social interaction linked to gaze detection.

### Gaze direction perception in Autism Spectrum Disorder

Autism Spectrum Disorder (ASD) is probably the best-known disorder in which abnormal eye contact is one of the main features (American Psychiatric Association, 2013). This is a neurodevelopmental condition which generates severe deficiencies in communication and reciprocal social interaction. Research has shown that, when looking at their environment, children with ASD tend to look downward and explore the environment with a wider lateral field of view than children with typical development (Noris et al., 2012). The same pattern of visual exploration for objects is observed in ASD and in controls (Mottron et al., 2007), and people with ASD are not different from controls in their ability to recognize objects such as cars and homes (López et al., 2004; Wallace et al., 2008; Wolf et al., 2008). Yet they exhibit different behavioral responses when they detect a direct gaze (Elsabbagh et al., 2012; Forgeot d'Arc et al., 2017; Jones & Klin, 2013; Pantelis & Kennedy, 2017; for a review, see Senju & Johnson, 2009b). More precisely, they direct their gaze towards that of others less spontaneously (Leekam et al., 1997) and have a tendency to look at the mouth region more than the eye region (Klin et al., 2002; Pelphrey et al., 2002). Various interpretations have been put forward to explain this difference. The hypothesis of passive insensitivity to direct gaze (Helminen et al., 2017; Lauttia et al., 2019; Moriuchi et al., 2017) was proposed after analyzing exploration patterns using eye tracking techniques with young children with ASD. It seems that when the task explicitly asks someone to look at someone else's eyes, children with ASD do not look further away from the eyes, and behave as typically developing children (Moriuchi et al., 2017). It is likely that children with ASD are not automatically attracted to the eyes as a salient stimulus and thus may subsequently show less interest in the gaze. Orienting to an eye stimulus is a controlled rather than an automatic process in ASD. On the other hand, a second hypothesis assumes that individuals with ASD exhibit active eye avoidance (Klin et al., 2003; Klin et al., 2009; Tanaka & Sung, 2016). This hypothesis suggests that the eyes are an emotionally charged region of the face that trigger an immediate visceral response and an increase in amygdala activity in individuals with ASD. They therefore avoid eye contact and focus on the external features (clothing, hair, hands) or other features and regions of the face (mouth, chin) as an adaptive and compensatory strategy. According to Tanaka and Sung (2016), this approach protects individuals with ASD from the discomfort and threat of the eyes. Thus, there is a fundamental difference between the two theories as the latter considers abnormal gaze detection and eye contact to be a top-down strategy, while the former sees them as a deficit in the (visual or social) salience of the eyes resulting in poor attraction of attention. Baron-Cohen(2000) considers that the ability to decode the direction of gaze may be intact in ASD but that difficulties arise from incorrect inference of the meaning of the eyes as a stimulus. This reasoning is slightly different reasoning from the other two as it places the locus of dysfunction beyond the perceptual processing of the eyes, just before the adoption of an active strategy to avoid eye contact. Recent research indicates that the key processes involved in coding gaze direction, namely the adaptation of neuronal responses to low-level perceptual processing of sensory information (e.g., the eyes), are intact in adults with ASD (Palmer, Lawson, et al., 2018b). In a study about divisive normalization in early visual processing, Rosenberg et al. (2015) demonstrated a reduction in sensory responses in the primary visual cortex. This observation could, in our opinion, for example be at the origin of a reduction in the representation of the distribution of luminance and consequently lead to an alteration of the coding of the direction of gaze in people with ASD.

An adaptation of the cueing paradigm (Posner, 1980) could help to disentangle the two hypotheses (salience hypothesis/active avoidance hypothesis). Participants could be required to quickly detect a target dot appearing close to one corner of an imaginary square centered at the point of fixation. This target could be preceded by the brief appearance, at the same location, of a face with direct gaze (i.e., the cue). The critical manipulation would concern the location of the target dot in relation the eyes: very close to the eyes, somewhere else on the

face, or outside the face. Another cue stimulus (e.g., a house) could replace the face in the control condition in order to ensure that the observed effects are face-specific. The response times for participants taken from the general population would be expected to be shorter for targets near the eyes as opposed to elsewhere. No variation in performance would be expected in the case of a nonfacial cue. This pattern would demonstrate preferential orienting to the eyes. However, if the salience hypothesis is correct, then the responses would not be expected to differ according to the location of the target, but also according to the cue type. People with ASD might be expected to exhibit slower response times than typically developing people for targets close to the eyes. Conversely, if the active avoidance hypothesis is correct, then the response pattern of ASD patients would be inverted compared with the controls. Response times to detect the target will be faster when it is moved away from the eye area. Again, no variation in performance would be expected in the case of a nonfacial cue.

From a neural point of view, based on fMRI evidence, Senju and Johnson (2009b) hypothesized that the detection and perception of direct gaze modulates the activation of the brain's social network. In fact, they suggest that atypical eye contact processing in ASD originates in the lack of influence of a subcortical face and eye contact detection route, which is hypothesized to modulate eye contact processing and guide its emergent specialization during development. Infants at high risk of ASD would exhibit atypical brain responses, which would suggest atypical modulation and/or synchronization of neural activities in response to perceived direct gaze. Anatomo-functional anomalies in the STS could constitute the first step in a cascade of neural dysfunctions underlying abnormal detection of gaze in ASD (Saitovitch et al., 2012). The use of the aforementioned cueing paradigm under fMRI could help validate this hypothesis.

## Gaze direction perception in schizophrenia

Another condition in which abnormal eye contact is studied is schizophrenia. The literature is inconsistent as far as the perception of the direction of gaze in schizophrenia is concerned. Some authors report no deficit (Franck et al., 1998, 2002; Kohler et al., 2008), while others do (Hooker & Park, 2005; Rosse et al., 1994; Tso et al., 2012; Tso et al., 2014). These discrepancies seem to be due to the variety of the methodologies used. Some research suggests that a bias in attribution of the gaze towards oneself is observed in schizophrenia. For instance, Tso et al. (2012) have shown that people with schizophrenia are more likely to say that other people are looking at them when they are not. They perceive ambiguous looks as being directed toward them, which may imply feelings of persecution. This bias increases with the severity of negative symptoms (Tso et al., 2012). Patients with paranoid symptomatology seem to assess the reliability of the person they are looking at differently depending on the direction of their gaze (Abbott et al., 2018). Other studies have shown no impairment in gaze perception in schizophrenia using a gaze cueing paradigm (Franck et al., 1998; Seymour et al., 2017). Seymour et al. (2017) suggested that the tendency to misjudge the direction of the gaze was due to the effects of the instructions for the task. In studies by Franck et al. (1998, 2002), participants were asked to decide whether the gaze was directed to the right or to the left. They also found that patients were slower when asked to judge whether the displayed face was looking at them or not. For instance, an instruction, such as "Is this person looking at you?" encourages them to judge the direction of gaze of others (Franck et al., 1998, 2002; Seymour et al., 2016), and may introduce response biases. Recently, it has been shown that gaze direction processing is intact in schizophrenia despite reduced performance in a theory of mind task (Palmer, Caruana, et al., 2018a). These results support the idea of Seymour et al. (2017) that people with schizophrenia have intact gaze direction perception and that the contradictory results are actually due to response biases produced by the tasks and instructions. In other words, these studies provide evidence in favor of a specific self-referential bias when the gaze is ambiguous, but no deficit when participants are requested to determine the direction of the gaze (for a review, see Bortolon et al., 2015). Observing a specific response bias when the gaze is ambiguous may suggest that this bias is the result of atypical functioning at the early processing levels, such as those involved in the processing of the contrast intrinsic to the eye (sclera vs. pupil). On the other hand, according to signal detection theory (Macmillan & Creelman, 2004), response biases may result from a different decision threshold relating to the direction of gaze, rather than from a change in lower-level sensory and perceptual processes. The discrepant results on gaze direction detection in schizophrenia found in the literature may therefore reflect differences in decision thresholds in people with schizophrenia caused by task instructions and/or their symptoms. For instance, patients with more severe negative symptoms (Tso et al., 2012) and signs of paranoia (Abbott et al., 2018) may be more likely to respond that someone is looking at them as a result of their symptomatology.

From a neural perspective, one study investigated the neural correlates of gaze perception in schizophrenia reported a decrease in activation in the frontal (e.g., bilateral inferior frontal), temporal (e.g., right tonsil, parahippocampal gyrus, bilateral spindle), occipito-parietal (e.g., bilateral occipital gyri), and subcortical areas in the patients studied (Kohler et al., 2008). Interestingly, the controls exhibited increased activation in the frontal and temporal regions with increased task difficulty, while the patients exhibited increased activation of the temporal regions, including the superior temporal gyrus. The superior temporal gyrus is part of the ventral frontal-parietal network that is believed to be responsible for

interrupting current processing and redirecting attention to a new focus (Corbetta et al., 2008). This has been linked to gaze processing, which may indicate heightened awareness of the gaze of others (Nummenmaa & Calder, 2009). Considering that patients have more difficulty determining the self-referential nature of gaze (Tso et al., 2012), it is possible that increased activation of the superior temporal gyrus for direct gaze in patients with schizophrenia may indicate increased awareness that another person is looking at them. Furthermore, increased activity in the pSTS was found when patients with schizophrenia looked at faces with neutral facial expressions. Yan et al. (2020) assumed that any hyperfunctioning of the right pSTS would result in an increased tendency to perceive neutral social stimuli as emotionally salient, or with intentions. We therefore suggest that increased activation of the pSTS may lead to an altered perception of other people's gaze direction and an altered interpretation of their intentions.

## Gaze direction perception in Social Anxiety Disorder

Relatively little attention has been paid to biases in gaze detection and perception in people with social anxiety disorder (SAD). This is particularly surprising, because SAD is related to intense feelings of being stared at by others, as well as to avoidance and fear of eye contact during social interactions (Schneier et al., 2011). The feeling of being stared at is even greater in SAD when faces are neutral or express a negative emotion (Horley et al., 2003, 2004). In addition, increased physiological arousal in SAD has been found for direct gaze versus averted gaze, suggesting that mutual gaze may be perceived as threatening (Baker & Edelmann, 2002). Studies using eye-tracking technology have supported these findings by demonstrating a smaller number of fixations and shorter fixation times on the eye region of faces with emotional expressions in people suffering from social phobia (Horley et al., 2003, 2004; Moukheiber et al., 2010). Other studies have shown that people with high levels of social anxiety fixate the eye region for a longer period of time, regardless of the direction of gaze, when the face has a neutral expression (Wieser et al., 2009). The visual exploration of the eye region of faces thus differs according to the expression of emotion on the face. Moreover, high social anxiety was associated with a wider cone of direct gaze (i.e., concept used to measure mutual gaze perception) across emotions in males (Jun et al., 2013; Schulze et al., 2013). Furthermore, Wieser et al. (2009) found that socially anxious and nonanxious women considered the averted gaze of neutral faces to be more unpleasant than a direct gaze, and averted gazes therefore may produce a reaction of motivational avoidance in people with SAD (Hietanen et al., 2008). This may be linked to the idea that looking away signals disinterest (Itier & Batty, 2009). These different results can be interpreted in light of cognitive models. The "eyes" stimulus is probably processed simultaneously *via*(i) an analysis that allows people suffering from SAD to extract this stimulus from the face, and (ii) another analysis allowing the extraction of perceptual information specific to the eyes (darker region/white region). In view of the aforementioned studies (Horley et al., 2003; Schneier et al., 2011; Wieser et al., 2009), it would seem that these information processing steps are not impaired in people suffering from social anxiety, even if no direct evidence of this has been found to date. On the other hand, the physiological reactions produced by the perception of gaze appear to be altered in SAD since averted gaze produces an avoidance reaction significantly different from that of individuals without SAD (Hietanen et al., 2008; Wieser et al., 2009). Future research should determine the locus of disturbance in the processing of gaze direction in SAD and related disorders.

From a neural point of view, Schneier et al. (2009) reported for the first time differences in neural activity associated with gaze behaviors in SAD. Their findings support the hypotheses of preferential activation of fear circuitry structures, such as the amygdala and insula, associated frontal regions (rostral anterior cingulate and medial prefrontal cortex), and core areas of visual face processing (e.g., the FG) in SAD in response to direct gaze. Eye-tracking findings did not differ significantly between groups in this study, but the direction of the nonsignificant differences was consistent with the hypothesis that SAD patients show greater gaze aversion in response to direct *vs* averted gaze. This is consistent with prior findings that SAD subjects avoid viewing the eye region (Horley et al., 2003). This suggests that, in SAD, the direction of gaze is directly related to fear responses and may simply constitute a sign of danger.

## Gaze direction perception in 22q11.2 Deletion Syndrome

Features of the autism spectrum are found in several pathogenic copy number variations, such as 22q11.2 deletion syndrome (22q11.2DS) (Vorstman et al., 2013). 22q11.2DS, one of the most common genetic syndromes (1/2000-1/4000 births), is one of the most robust genetic risk factors for schizophrenia (1-2% of cases). It has been suggested that the high prevalence of autistic behaviors in children with 22q11.2 deletions should not be viewed as ASD, but rather as prodromal symptoms preceding the onset of schizophrenia (Eliez, 2007; Karayiorgou et al., 2010; Van et al., 2017; Vorstman et al., 2006). Approximately 30% of patients with 22q11.2DS develop psychotic symptoms in adolescence or early adulthood (Monks et al., 2014). Anxiety disorders also are frequent (35% of children and 27% of adults), often expressed in the form of simple phobias (fear of the dark, fear of animals, fear of thunderstorms, etc.) or a social phobia (Philip & Bassett, 2011). Difficulties in social relationships with peers are a

common complaint among school-aged children with 22q11.2DS. It is well established that children and adults with 22q11.2DS have poorer social skills compared with typically developing young people, particularly in recognizing emotions on faces and in voices, as well as understanding the emotions involved in scenes depicting social interactions (Campbell et al., 2015; Leleu et al., 2016; Peyroux et al., 2020). Underlying impairments in social cognitive processes might be partially responsible for these social dysfunctions (for a review, see Norkett et al., 2017) and could be linked to a diagnosis of psychosis (Jalbrzikowski et al., 2012; Morel et al., 2018). Interestingly, although some authors suggest that the overall exploration pattern of a face is abnormal in 22q11.2DS, an analysis of error patterns has shown that 22q11.2DS patients more frequently mistake sadness for fear, surprise for happiness, and disgust for surprise (Peyroux et al., 2020). The authors suggest this confusion is related to visual details of the faces. For instance, the configuration of the eyes and eyebrows may explain why sadness is mistaken for fear and disgust for surprise. This analysis provides some indirect clues as to how 22q11.2DS patients process the region of the eyes. To our knowledge, however, there are no data in the literature on gaze direction detection and perception in 22q11.2DS. From a clinical point of view, it seems that very early on in their development, certain children carrying 22q11.2DS exhibit atypical behavioral responses to the detection of the gaze of others, such as eye contact avoidance. They also sometimes have the impression that they are being looked at when this is not the case, just like people with paranoid traits. There is, therefore, a pressing need to better investigate and understand the specific pattern of the gaze direction detection in this pathology and how it influences social cognition and behavior. One possibility is that the paranoid symptomatology (Schneider et al., 2017) and social phobia (Philip & Bassett, 2011) observed in 22q11.2DS are at least partly due to misperception or misinterpretation of gaze direction. To our knowledge, from a neuronal point of view, there is very little specific literature.

## Conclusion and future directions

In this narrative review, we first focused on the detection and perception of gaze direction by combining the associated behavioral and neural responses. Certain disturbances in which difficulties in gaze detection are found were then also reviewed, in order to better understand how the particularities of information processing might negatively impact social relations.

Several behavioral models have been proposed to explain the perception of direct or averted gaze (Baron-Cohen, 1995; Morton & Johnson, 1991; Simion & Giorgio, 2015). Although at first sight these models appear to be contradictory, combining them provides a better understanding of the various processes underlying the detection of the direction of gaze. However, there are still a number of grey areas. As far as behavior is concerned, these uncertainties concern: (a) the time course of visual information processing (eyes first or face first), and (b) the hypothesis of salience priority, i.e., if the visual contrast between facial features defines preferential orienting. As far as pathological conditions are concerned, questions remain regarding: (a) the hypothesis of passive insensitivity to gaze in people with ASD, (b) the hypothesis of active avoidance of gaze in people with ASD, as well as (c) the level of gaze treatment deficit in people with schizophrenia. These issues should be the focus of future research, and we have made some suggestions about how to investigate the hypotheses and theoretical models. Obviously other paradigms are possible.

At the neural level, different networks seem to allow both the detection of a gaze and, more precisely, the perception of direct gaze versus diverted gaze. Although the data are not certain, a specialized system seems to exist, including several hubs dedicated to different aspects of information processing. The pathway through which the amygdala is involved in the nonconscious perception of gaze remains to be explored. Unraveling whether its activation is due to feedback from the striate cortex or to input from the superior colliculus and the pulvinar could provide insights into the role of the subcortical route in the feeling of being stared at. In the same way, the role of the frontal areas should be looked at more closely. We might find that this structure does not play a prominent role in gaze detection and perception, but that it is recruited because of its role in joint attention, emotional decoding, and theory of mind (Ingvar & Franzén, 1974; Lee et al., 2004). Indeed, a link seems to have been established between the perceived direction of gaze and the neuronal processing of social decision-making(Sun et al., 2018). This could lead to a novel explanation for mistaken gaze direction (sometimes found) in schizophrenia, which is known to be a neurodevelopmental hypo-frontal condition. We could hypothesize that impaired theory of mind due to frontal dysfunction leads to the misattribution of gaze direction, rather than the misattribution of gaze perception leading to paranoid symptoms. One last grey area at the neuronal level concerns coordination between the two cerebral hemispheres. We have suggested a number of ways of testing the different hypotheses, but other paradigms could be used, of course.

Overall, we believe that we have clearly demonstrated the importance of better understanding the different stages in the processing of information related to gaze detection and perception. Future research should focus on the aforementioned areas of ongoing debate to better establish how the social brain develops and works, taking the detection of another person's gaze as the starting point. An improved understanding of these processes and their development would make it possible to offer early and adapted care to the disturbances observed. Improved brain activation in facial treatment networks has already been demonstrated after specific cognitive

remediation for the recognition of facial effects (Bölte et al., 2015), specifically in the eye region (Karagöz-Üzel et al., 2018). It is therefore possible that gaze direction reeducation would have an impact on the neurodevelopmental cascade of the construction of the social brain.

## Declarations

**Conflicts of interests** The authors declare that they have no competing interests.

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# Le déroulement temporel de la perception du regard

La revue systématique de littérature exposée précédemment a permis de discuter des bases théoriques de la détection et de la perception de la direction du regard. Il est clairement établi que le regard direct, dirigé vers l'observateur, est un signal social extrêmement saillant (George & Conty, 2008; Hamilton, 2016). Toutefois, cette revue a montré que plusieurs zones d'ombre restaient à éclaircir. Que regardons-nous en premier lorsque nous sommes face à un visage ? Sommes-nous attirés directement par les yeux en faisant abstraction du reste du visage, est-ce le contraire ou bien sommes-nous en mesure d'analyser l'ensemble du visage de manière simultané ?

Ainsi, l'objectif de l'Étude 2 a été de comprendre le déroulement temporel du traitement de l'information lors de la perception de la direction du regard. Pour cela, une expérience de jugement de la direction du regard a été proposée à des étudiants. Cette expérience se composait de visages où un décalage temporel, non perçu consciemment, était introduit entre la présentation des yeux et le reste du visage de sorte que les yeux soient présentés avant le visage, après le visage ou bien que les deux soient présentés simultanément. La tâche consistait à porter un jugement sur la direction du regard, c'est-à-dire qu'il était demandé aux participants d'appuyer sur une touche spécifique aussi vite que possible lorsque le regard était dirigé vers eux, et sur une autre touche, toujours aussi vite que possible, lorsque le regard était dirigé ailleurs.

# The time-course of information processing during eye direction perception

Marie-Noëlle BABINET, Caroline DEMILY, Eloïse GOBIN, Clémence LAURENT, Thomas MAILLET & George A. MICHAEL

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**Abstract**

Gaze directed at the observer (direct gaze) is a highly salient social signal. Despite the existence of a preferential orientation towards direct gaze, none of the studies carried out so far seems to have explicitly studied the time-course of information processing during gaze direction judgment. In an eye-direction judgment task, participants were presented with a sketch of a face. A temporal asynchrony was introduced between the presentation of the eyes and that of the rest of the face. Indeed, the face could be presented before the eyes, the eyes could be presented before the face, or the face and the eyes could be presented simultaneously. The results suggest that the time-course of information processing during eye direction judgment follows a continuum that makes it possible to perceive the eyes first and then to use the facial context to judge the direction of gaze. Although these results are discussed in the light of existing theories about the mechanisms underlying gaze processing, our data provides new information suggesting that, despite their power to capture attention, the eyes probably have to stand out from a more general spatial configuration (i.e., the face) in order for their direction to be adequately processed.

**Keywords**: time-course, gaze processing, averted gaze, direct gaze, attentional capture

## 1. Introduction

Gaze directed at the observer (direct gaze) is a highly salient social signal with multiple effects (George & Conty, 2008; Hamilton, 2016). Preferential orientation toward direct gaze seems to be present soon after birth (Hietanen, 2018). Baron-Cohen (1994) suggested the existence of a specific visual context that maintains spatial relationships between facial components and

makes it possible to identify gaze direction. For instance, newborns appear to track moving face-like patters longer than they do a scrambled face or a blank face (Johnson et al., 1991). Other studies (Farroni et al., 2006; Tomalski et al., 2009) found that a discrimination difference between direct and averted gaze was observed in children and adults only when the face was presented straight (classic facial configuration) vs. upside-down face. An additional argument in favour of Baron-Cohen's theory (Baron-Cohen, 1995) is when only the eyes were presented, no difference was observed in the time taken by the participants to judge the direction of gaze, whereas this was the case when the whole face was presented (Ricciardelli & Driver, 2008).

An alternative view (Batki et al., 2000; Langton et al., 2000; Simion & Giorgio, 2015) has been proposed to explain newborns' preferences for direct gaze. These authors suggested that this preference is due to domain-general attentional biases toward the specific structural properties of the features present in a face (i.e., the eyes). This type of general attentional bias probably derives from the functional properties of the newborns' immature visual system (Simion & Giorgio, 2015). From the age of 4 months, children seem to be sensitive to the contrast polarity that results from the typical perceptual patterns of the eyes, i.e., the black pupil on a white sclera (Michel et al., 2017). In adults, gaze direction judgments might possibly be based on the outcome of competition between different gaze direction signals, such as luminance cues and geometric cues (Babinet et al., 2022; Olk et al., 2008). From an evolutionary point of view, the extraction of properties of the eye region can lead to a gradual construction of a representation of gaze (Farroni et al., 2003).

It seems fairly obvious that these theories are not necessary mutually exclusive. It is possible that there are specific eye and gaze detection mechanisms based on a facial context constituted by facial features. Based on Baron-Cohen's argument (Baron-Cohen, 1994, 1995) that the eyes

constitute a well-defined area with specific regions of contrast, i.e., a darker region (iris/pupil) and a brighter region (the sclera), we can make the following hypothesis (Babinet et al., 2022): it is possible that there is a processing step specific to the "eye" stimulus integrated within a more general spatial context (i.e., the face). This specific processing of the eyes might then extract specific perceptual information from the eye region (dark/bright contrasts) and this contrast would determine the salience of this region (Babinet et al., 2022; Baron-Cohen, 1994, 1995).

The above works implicitly suggest that there is a time-course of information processing during gaze direction detection. For instance, by assuming that gaze direction discrimination requires the presence of a facial context, Baron-Cohen (1994, 1995) explicitly suggests that the face is processed first. At the same time, Simion and Giorgio (2015) suggest that there are specific processes for the eyes and this may imply that they are processed independently of the face, either at the same time as it or before it. To our knowledge, no study to date has tried to clarify this issue directly.

Here, we try to shed some light on the time-course of information processing during gaze direction detection and discrimination and, therefore, to determine which of the above-mentioned hypotheses is closest to reality. To do this, we proposed a task in which adult participants were presented with the sketch of a face and were required to make an eye-direction judgment (i.e., the eyes are looking at me *vs.* they are looking away) as quickly and as accurately as possible. A temporal asynchrony was introduced between the presentation of the face and that of the eyes and eyebrows in such a way that the whole face appeared (a) face first then eyes, (b) eyes first then face, or (c) simultaneously. By recording the response times (RT), we were able to assess whether processing of direct gaze (as compared to averted gaze) was most

evident when the face came first, when the eyes came first, or when the eyes and the face appeared simultaneously. Since we hypothesized that priority would be given to the eyes during processing (1st hypothesis), we expected RT to be faster when the eyes appeared first. In addition, slower RT were expected when the face appeared first, since this would run counter to the hypothesized natural time-course of gaze detection processing. Given this hypothesis, and according to the literature (Baron-Cohen, 1994, 1995; Ricciardelli & Driver, 2008), even though faster responses were expected when the eyes were presented first, we did not expect to observe any judgment of gaze direction since the spatial context of the face is necessary for such judgments. According to the hypothesis that the processing of the face will be prioritized (2nd hypothesis), faster RT were expected when the face appeared first. Moreover, since some theories hold that the judgment of gaze direction is based on the interpretation of the facial context (Baron-Cohen, 1994, 1995; Riechelmann et al., 2021), we expected to observe a difference between direct and averted gaze.

## 2. Method

### 2.1 Participants

Eighty-three students from the University of Lyon participated in the experiment (50 women and 33 men; mean age = 22.63; SD = 1.92 years; mean number of years of education = 13.55; SD = 1.66 years). All reported normal or corrected-to-normal vision and were unaware of the precise aim of the experiment. All participants gave their written informed consent and the study was conducted in accordance with the Declaration of Helsinki.

### 2.2 Apparatus and stimuli

Stimuli consisted of sketches of a face drawn in black (mean luminance of 5 measures = 0.21 cd/m$^2$, SD = 0.03) presented on a gray background (mean luminance of 5 measures = 156.24 cd/m$^2$, SD = 2.17) using GIMP version 2.10 software. Two eye direction conditions were created: (1) direct gaze, in which the face was gazing directly at the participant; (2) averted gaze, in which the face was gazing to the right or left at an angle of 60° from the midline. The stimuli represented a full face, were presented in the center of the screen and covered a visual angle of 9.9° x 12.7° (width × height) at a viewing distance of 40cm. The angular distance between the two eyes (center to center) was 3.7° and the angular distance between the fixation cross and the center of each eye was 2.9°. The fixation cross was presented in the center of the screen and measured 1.43° x 1.43°. All instructions and stimuli were presented on a 15-inch screen, with a resolution of 1920x1080 pixels. Stimulus presentation, timing and data collection were controlled by OpenSesame (Mathôt et al., 2012). The experiment was conducted on a DELL computer equipped with an *Intel® UHD Graphics 620* card and took place in a normally lit and quiet room.

### 2.3 Procedure

A trial started with the presentation of a fixation cross for 1500ms. This was followed by the presentation of a face, centered at the fixation point. Temporal asynchronies were introduced between the presentation of the face (face contour, nose and mouth) and the eyes (eyes and eyebrows) to create five conditions: -100ms (eyes first), -50ms (eyes first), 0ms (eyes and face at the same time), +50ms (face first), +100ms (face first). The whole face was therefore presented in an eyes-face order (-100ms, -50ms), eyes and face simultaneously (0ms) and in a face-eyes order (+50ms, +100ms) (see Fig. *1*). The direction of gaze (direct *vs.* averted) was

also manipulated in such a way that the combination of the two factors (i.e., gaze direction and SOA) resulted in 10 conditions. The participants were told that they would see faces appear on the screen. They were asked to press the C key as quickly as possible if the eyes were looking at them and the N key if the eyes were looking away. The stimuli remained present on the screen until a response was given. Each participant completed one experimental block consisting of 300 trials (30 trials per gaze direction per SOA). Gaze direction and SOA were presented in a completely random and equiprobable order and the condition for each new trial was chosen automatically by the computer. Once the participant had heard the instructions, the experiment could begin. The participant could press any key to start. RT and errors were recorded by the computer program. At the end of the experiment (which lasted about 10 minutes), a screen was displayed to thank the participants and tell them that the experiment was over. The participants were then debriefed. No training session was conducted.

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INSERT FIGURE 1 HERE PLEASE

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### 2.4 Design and analysis

RT were defined as the latency from the onset of eye presentation until the first key press. After removing error trials (3.33% of the data), we additionally excluded trials with anticipatory responses (RTs < 150 ms; corresponding to 0.32% of the remaining data). After that, all RT outliers larger than 2SDs were removed for each participant (corresponding to 4.25% of the remaining data).

Separate repeated-measures analyses of variance (ANOVAs, $\alpha = .05$, throughout) with the SOA (-100ms, -50ms, 0ms, +50ms, +100ms) and gaze direction (direct *vs.* averted) as within-participants factors were conducted to analyze correct RT. Multiple *post-hoc* comparisons were conducted using the Scheffe test. Effect sizes were expressed as partial eta squared. Statistics were computed using JASP (JASP Team, 2022). The error rate was not analyzed since it was lower than 5%.

## 3. Results

A significant gaze * SOA interaction effect was observed, $F(4,328) = 16.31$, $p < .001$, $\eta^2_p = .17$ (see Fig. *2*). When direct and averted gaze were compared with the Scheffe *post-hoc* test, significant differences in RT were found at +50 (direct: mean = 564ms, SD = 88ms; averted: mean = 528ms, SD = 95ms; $p < .001$) and +100ms (direct: mean = 550ms, SD = 83ms; averted: mean = 504ms, SD = 102ms; $p < .001$). No significant differences in the RT were found at -100, -50ms or 0ms. For detailed results, see Table *1*.

As far as direct gaze was concerned, significant differences in RT were found between -100 (mean = 491ms, SD = 96ms) and -50 (mean = 537ms, SD = 88ms; $p < .001$), -100 and 0 (mean = 531ms, SD = 91ms; $p < .001$), -100 and +50 (mean = 564ms, SD = 88ms; $p < .001$), -100 and +100 (mean = 550ms, SD = 83ms; $p < .001$), -50 and +50 ($p < .001$), 0 and +50 ($p < .001$) and, finally, between 0 and +100 ($p < .05$) .

As far as averted gaze was concerned, significant differences in RT were found between -100 (mean = 480ms, SD = 107ms) and -50 (mean = 520ms, SD = 104ms; $p < .001$), -100 and 0

(mean = 523ms, SD = 101ms; $p < .001$), -100 and +50 (mean = 528ms, SD = 95ms; $p < .001$), -100 and +100 (mean = 504, SD = 102ms; $p < .001$), 0 and +100 ($p < .05$) and, finally, between +50 and +100 ($p < .001$).

It is interesting to note that, for the averted gaze, it was necessary to wait until +100 after the presentation of the face to observe an effect, while the effect was already observed at +50 and persisted at +100 for direct gaze.

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INSERT FIGURE 2 HERE PLEASE

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INSERT TABLE 1 HERE PLEASE

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## 4. Discussion

To shed light on the time-course of information processing during gaze direction discrimination, participants were presented with a sketch of a face and were required to make an eye-direction judgment. Using a temporal asynchrony between the presentation of the face and the eyes, our results show that gaze direction judgment varies depending on the asynchrony that has been introduced. Regardless of gaze direction, participants exhibited faster responses when the eyes appeared 100ms before the face. With regard to the paradigm (i.e. a gaze judgment), presenting the eyes without any other stimulus would incite participants to direct their attention to the point at which they are located (Posner, 1980, 2016). The absence of any other information at that location may well explain these faster responses. However, the same

effect was no longer visible at -50ms, meaning that this effect occurs in a delimited time window and that the system requires at least 100ms to perform this rapid orientation. This is highly consistent with the model proposed by Müller and Findlay (1988), which suggests the existence of an early automatic spatial orientation mechanism, and also tallies well with the idea that the eyes may capture attention when presented on their own as a stimulus (Burra & Kerzel, 2021). Perceptual salience created by local contrasts of the eyes - a darker region (iris/pupil) and a white region (the sclera) (Baron-Cohen, 1995) - is likely to attract attention, be accorded processing priority and lead to faster responses (Babinet et al., 2022). Our visual system is able to find the item in the visual field which differs the most from the others in terms of salience (here, the eyes) and which it is therefore likely to be most important to select for further analysis (Theeuwes, 1992). This result is also in line with the theory of Simion & Giorgio (2015), who propose that the eyes are processed either independently of the face or, indeed, before the face. One other finding was that when the eyes appeared first or when the eyes and the face appeared simultaneously, no differences were observed between direct and averted gaze. This is also in line with the hypothesis that something more than the mere presence of the eyes, i.e., a context (Baron-Cohen, 1994), is required if participants are to judge gaze direction. These initial data seem to imply that the gaze is processed very early and quickly, regardless of its direction, thus confirming the 1st hypothesis.

When the face appeared first, differences between direct and averted gaze were found. This suggests that information available in the face is necessary for gaze direction discrimination, thus partially confirming the 2nd hypothesis. It has already been hypothesized that the face creates a spatial context that permits the enhanced processing of gaze direction (Adams & Kleck, 2005; Baron-Cohen, 1994, 1995; Burra & Kerzel, 2021). According to Morton & Johnson (1991), there is a process named *Conspec* configured to detect the faces of

conspecifics. The effectiveness and ubiquity of the simple T-shaped schematic face (i.e., the spatial context of the two eyes, the nose and the mouth) suggest that faces may be detected by means of a simple template-like process (Riechelmann et al., 2021; Tsao & Livingstone, 2008). The differences we found between direct and averted gaze were to the detriment of direct gaze. This detection started as early as 50ms after the presentation of the face and remained stable up to 100ms. Responses to direct gaze were overall slower than to averted gaze, and this may be due to the paradigm we used. Indeed, a number of studies have shown that humans are biased to detect direct gaze faster than averted gaze (Conty et al., 2006, 2007; George et al., 2001; von Grünau & Anston, 1995), a phenomenon referred to as the "stare-in-the-crowd" effect. The experimental paradigms used in these studies were different from ours. For instance, these studies used visual searches for one target among others (Conty et al., 2006), gender judgment (male *vs.* female face) and other techniques (George et al., 2001). However, other studies have found a deceleration of RT similar to the one observed here for direct gaze, thus indicating an advantage of averted gaze (Riechelmann et al., 2021). These results suggest that presentation conditions and task demands play an important role in gaze direction discrimination. What is new in our results is that the difference between gaze conditions appeared only in situations when the eyes were added to a sketch of a face, but never the other way around. This strongly suggests that, despite their ability to capture attention (Burra & Kerzel, 2021), the eyes probably have to stand out from a more general spatial configuration (i.e., the face) in order for their direction of gaze to be adequately processed.

The observation that the effect we report appeared at +50ms suggests that the direction of gaze is processed rapidly, and this tallies well with the fact that it takes less than 70 milliseconds to adjust the focus of attention to a new stimulus (Benso et al., 1998). The fact that this effect remains virtually unchanged at +100ms may suggest that, following the processing of gaze

direction, attention remains focused on it for some more time. It is known that attention may remain voluntarily focused on a stimulus for up to 500 milliseconds (Benso et al., 1998). It is impossible to know if this time window is the same in the case of gaze fixation since our paradigm only used SOAs up to 100ms. Future research could shed some light on this issue.

When examined in more detail, our results suggest that different processes might be dedicated to the processing of direct gaze (as seen through the rapid deceleration of RT at +50ms) and averted gaze (as seen through the acceleration of RT at +100ms), and each would have its own time-course. In the case of the former, it is possible that the processing of a direct gaze that stands out from a face starts very quickly and may be due to an inability to disengage attention from a mutual contact (Burra & Kerzel, 2021) or a voluntary continued concentration of attention on the eyes. With regard to the latter, the processing of an averted gaze may start later and trigger a shift of attention toward the direction in which the eyes are looking (i.e., joint attention; see Frischen et al., 2007, for a review on gaze cueing). Let us imagine that we see somebody looking directly at us. Such a mutual contact would trigger physiological arousal (Hood et al., 2003; Kampe et al., 2001; Kawashima et al., 1999; Senju & Johnson, 2009) and rapid processing of their eyes and a freezing-like reaction would follow. Becoming aware that the gaze is not really directed towards us but somewhere else (i.e., we are not the target of that person's attention) would lead to attentional disengagement and a faster response towards the direction of the joint target (Wang et al., 2019).

Our study has some limitations that should be highlighted. First, the type of stimulus used here, namely the sketch of a face, does not resemble real stimuli (such as photographs). Nevertheless, one of reasons for this choice was to optimize our control of all aspects of the stimuli and avoid the typical problems that natural stimuli give rise to (i.e. contrast, saliency, visual complexity).

Moreover, the use of drawings minimizes confounds related to facial characteristics that are present in natural photographs, i.e. gender, age, attractiveness, and ethnicity, as well as physical characteristics such as wrinkles and freckles (Peyroux et al., 2020). Another limitation concerns the ratio of male: female participants. It seems legitimate to inquire about the extent to which gender impacts gaze detection (Shi et al., 2020).

## 5. Conclusions

It appears that the eyes are the first facial element to be detected but that information about the gaze direction is not immediately available. The perceptual salience created by the local contrasts of the eyes is likely to attract attention in an automatic way, be assigned processing priority and lead to faster responses. Subsequently, the face creates a spatial context which favors the processing of gaze direction. Finally, our results suggest that different processes might be dedicated to the processing of direct gaze and that of averted gaze, each having its own time-course.

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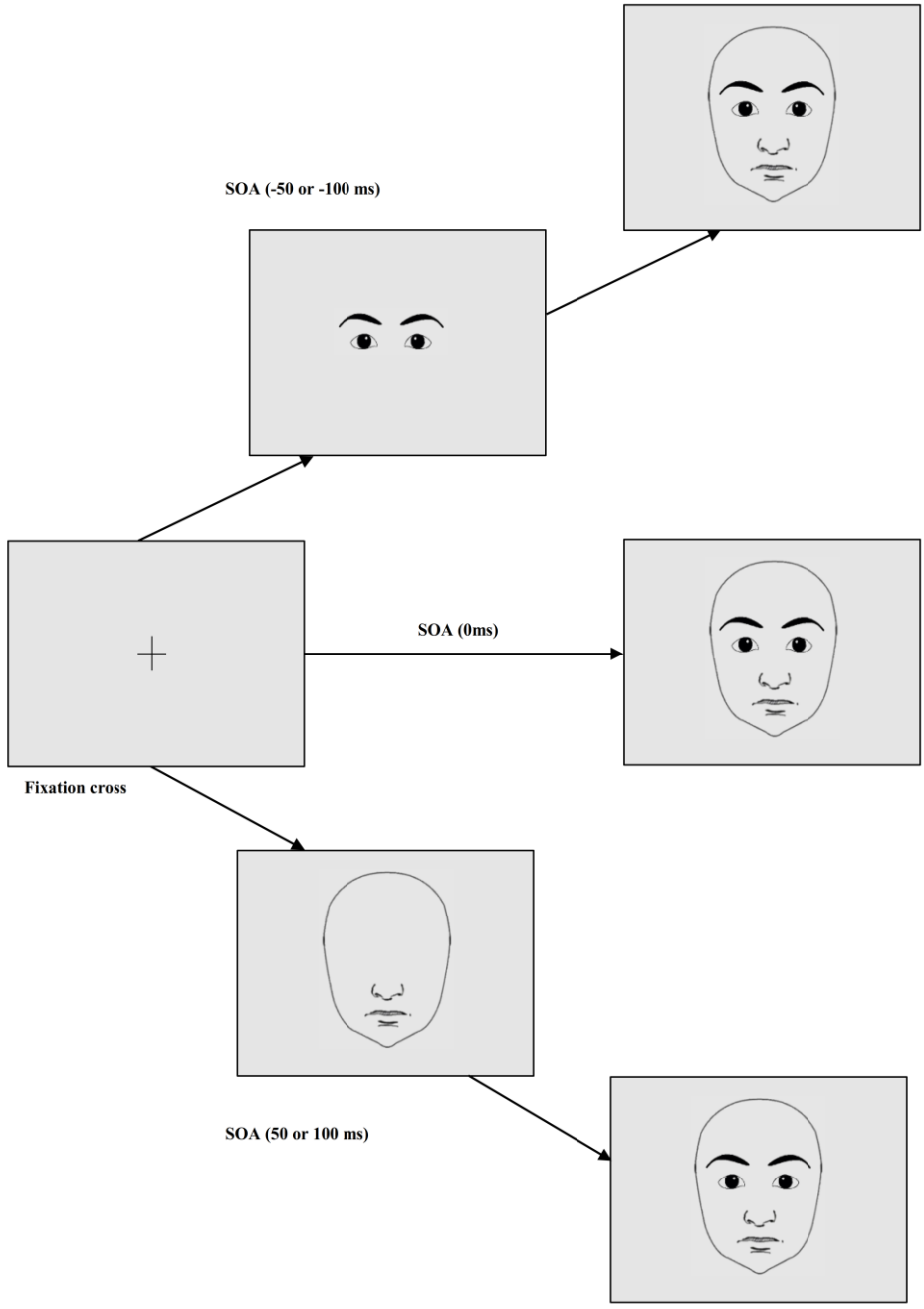


Fig 1. Illustration of experimental stimuli and procedure for the direct gaze condition.

It can be seen that the whole face was presented in an eyes-face order (-100ms, -50ms), eyes and face simultaneously (0ms) or in a face-eyes order (+50ms, +100ms). Response times were defined as the latency from the onset of eye presentation until the first key press.

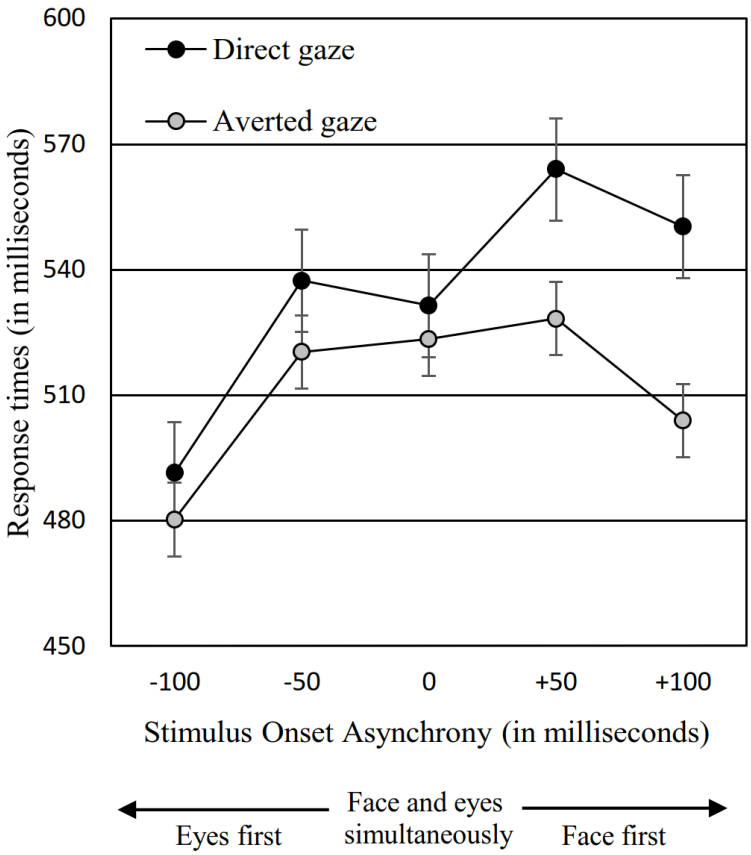


Fig 2. Mean Responses times (RTs) as a function of gaze direction (direct *vs.* averted gaze and SOA (-100ms vs. -50ms vs. 0ms vs. +50ms vs. +100ms). Error bars represent 1 standard error.

Table 1. *post-hoc* comparisons of gaze type * SOA of interest.

| | **-100ms direct gaze (mean=491; SD=96 ms)** | **-50ms direct gaze (mean=537; SD=88 ms)** | **0ms direct gaze (mean=531; SD=91ms)** | **+50ms direct gaze (mean=564; SD=88 ms)** | **+100ms direct gaze (mean=550; SD=83 ms)** | **-100ms averted gaze (mean=480; SD=107 ms)** | **-50ms averted gaze (mean=520; SD=104 ms)** | **0ms averted gaze (mean=523; SD=101ms)** | **+50ms averted gaze (mean=528; SD=95 ms)** | **+100ms averted gaze (mean=504; SD=102 ms)** |
|---|---|---|---|---|---|---|---|---|---|---|
| **-100ms direct gaze (mean=491; SD=96ms)** | / | | | | | | | | | |
| **-50ms direct gaze (mean=537; SD=88ms)** | < .001* | / | | | | | | | | |
| **0ms direct gaze (mean=531; SD=91ms)** | < .001* | .99 | / | | | | | | | |
| **+50ms direct gaze (mean=564; SD=88ms)** | < .001* | <.001* | <.001* | / | | | | | | |
| **+100ms direct gaze (mean=550; SD=83ms)** | < .001* | .47 | .03* | .38 | / | | | | | |
| **-100ms averted gaze (mean=480; SD=107ms)** | 0.96 | / | / | / | / | / | | | | |
| **-50ms averted gaze (mean=520; SD=104ms)** | / | .63 | .97 | / | / | <.001* | / | | | |
| **0 averted gaze (mean=523; SD=101ms)** | / | / | .99 | / | / | <.001* | 1 | / | | |
| **+50ms averted gaze (mean=528; SD=95ms)** | / | / | / | <.001* | / | <.001* | .95 | .99 | / | |
| **+100ms averted gaze (mean=504; SD=102ms)** | / | / | / | / | <.001* | <.001* | .13 | .02* | <.001* | / |

Asterisks denote significant differences ($p \leq 0.05$).

# La perception du regard dans un contexte de maladie rare

A travers la littérature, les chercheurs ont mis en évidence l'importance de la région oculaire dans la transmission d'informations nécessaires à la reconnaissance des émotions, en plus de son rôle crucial dans la perception de la direction du regard (Ekman & Friesen, 1978; Itier & Batty, 2009; Liang et al., 2021). Prenons l'exemple où une personne vous regarde dans les yeux en exprimant une émotion de peur. Il est probable que vous perceviez alors une menace et que vous ayez un comportement de fuite. La combinaison de la direction du regard et de l'émotion permet de percevoir des conduites d'approche et d'évitement (Adams & Kleck, 2003, 2005). Etant donné l'importance de la perception du regard et des émotions dans nos interactions sociales, via la communication non-verbale, il est assez facile d'imaginer que des troubles de la cognition sociale soient observés dans différents troubles psychiatriques telles que la schizophrénie ou chez les personnes à haut risque de psychose (comme les enfants porteurs de la délétion 22q11.2) (Jalbrzikowski et al., 2012; Tor et al., 2018). Bien qu'il soit clairement établi dans la littérature que les enfants porteurs d'un 22q11.2DS présentent des compétences sociales plus faibles que les enfants neurotypiques, en particulier dans la reconnaissance des émotions faciales, aucune étude spécifique ne s'est intéressée à la perception du regard qu'il soit émotionnel ou non chez ces enfants.

Pour éclaircir cet aspect, nous avons créé une tâche dans laquelle les enfants se sont vus présentés un paradigme *oddball* comportemental avec trois types de stimuli différents : des formes géométriques, des regards non émotionnels et des regards émotionnels. Pour chaque type de stimuli, deux conditions étaient proposées : des stimuli rares parmi des stimuli fréquents. Les enfants devaient appuyer le plus rapidement possible sur une touche réponse pour chaque stimulus. Afin de contrôler des réponses anticipées et d'évaluer le contrôle inhibiteur face au regard, des stimuli No-Go ont été ajoutés à la tâche. L'article exposé ci-après ne présente que des données préliminaires, la collecte de données n'étant pas achevée.

# Gaze perception with and without emotion in 22q11.2DS

Marie-Noëlle BABINET, Eloïse MASOERO, Laurette TRINCKQUEL, Caroline DEMILY,

& George A. MICHAEL

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Article retranscrit en version manuscrite

**Abstract**

The eyes and the gaze are important stimuli for social interactions in humans. The eye region carries information necessary for emotion recognition and is thus central to non-verbal communication. 22q11.2 deletion syndrome (22q11.2DS) is considered as a valuable, simplified biological model for studying early neuropsychiatric disorders. Certain psychiatric disorders exhibit social cognition disturbances but, as far as 22q11.2DS in concerned, there is no data in the literature on gaze direction perception and detection. This study will attempt to shed light on this aspect. Twenty-three children with 22q11.2DS and thirty-three matched healthy controls completed a behavioral *oddball* paradigm in which they had to press a button each time a stimulus was presented. Three types of stimuli were used: geometrical figure, gaze, and emotional gaze. For each type of stimuli, the stimuli were subdivided in rare (10% occurrence) and frequent (80% occurrence). Furthermore, NoGo stimuli (10% occurrence) were added. The results show that the eyes are a special cue but that the atypical processing of the information conveyed comes mainly from an effect of the emotion associated with the gaze. A lack of inhibition seems to be an important marker and could be linked to the presence of psychotic symptoms in 22q11.2DS but also in the general population.

**Keywords**: gaze perception; emotional gaze; 22q11.2DS; inhibition

## 1. Introduction

Gaze direction is a useful signal since it directly provides information on the person's interest and the presence of possible dangers nearby (Emery, 2000). It is well-established that infants are attracted to faces early in life, and research has tried to unravel the impact on newborns' attention and behavior on the detection and perception of gaze directed at them (direct gaze) or away from them (averted gaze). The earliest studies (Hood et al., 1998; Vecera & Johnson, 1995) already showed different behaviors in newborns in these two conditions, with a preferential orientation toward direct gaze. Preferential orientation for direct gaze can help build a certain number of relational capacities (Itier & Batty, 2009), may constitute an early sign of the emergence of social interactions and may prime autonomous physiological activity (Hietanen, 2018). This preferential orientation is supported by various theories. Baron-Cohen (1994) suggested the existence of a specific visual context that maintains spatial relationships between facial components and makes it possible to identify gaze direction. An alternative view (Batki et al., 2000; Langton et al., 2000; Simion & Giorgio, 2015) suggested that this preference is due to domain-general attentional biases toward the specific structural properties of the features present in a face (i.e., the eyes). Babinet and colleagues (2022) assume that they can be integrated into a more general framework. For example, eye detection and perception may include a pictorial encoding step extracting detail from lighting, grain, and high contrast salient areas of the face. This captures the static pose and expression seen on a face (Bruce & Young, 1986).

In addition to its important role in gaze direction perception, the eye region carries information necessary for emotion recognition (Bindemann et al., 2008; Ekman & Friesen, 1978; Itier & Batty, 2009; Liang et al., 2021) and is thus central to non-verbal communication.

For example, angry people often stare straight into the eyes of the person with whom they are trying to quarrel or fight, and timid people who fear others may drop their eyes and look away. Previous research has found that when gaze direction matches the underlying behavioral intent (approach/avoidance) communicated by an emotional expression, the perception of that emotion is enhanced or facilitated (Adams & Kleck, 2003, 2005). It has been argued that proximity-oriented emotions such as happiness, love, and anger tend to be expressed through direct vision, while avoidance-oriented emotions such as jealousy, sadness, and disgust are more likely to be communicated by avoidance (Argyle et al., 1994; Kleinke, 1986; Sander et al., 2007). For example, angry faces are detected faster and perceived with greater intensity when the expresser's gaze is directed toward the observer rather than away, while an averted gaze enhances the perception and detection of fearful faces (Rigato et al., 2013) and sad faces (Adams & Kleck, 2003).

Given the importance of gaze direction perception and emotion perception for social interactions (for a review, see Norkett et al., 2017), it is not surprising that psychiatric conditions like schizophrenia and particularly persons who have a high risk of psychosis (Jalbrzikowski et al., 2012; Morel et al., 2018; Tor et al., 2018), exhibit social cognition disturbances (Cañadas & Lupiáñez, 2012). Features of schizophrenia are found in several pathogenic copy number variations such as 22q11.2 deletion syndrome (22q11.2DS) (Vorstman et al., 2013). It is well established that children and adults with 22q11.2DS have poorer social skills compared to typically developing young people, particularly in recognizing emotions on faces and in voices, as well as understanding the emotions involved in scenes depicting social interactions (Campbell et al., 2015; Leleu et al., 2016; Peyroux et al., 2020). To our knowledge, however, there are no specifically data in the literature on gaze direction perception and detection in 22q11.2DS. Given that social cognition is affected in 22q11.2DS, we can ask whether this is at least partly due to disturbed gaze perception, whether expressing an emotion

or not. The literature on schizophrenia shows that gaze perception and emotional facial expressions interact (Pinkham et al., 2011). Various authors propose that the perception of a direct gaze suggesting threat leads to misattribution of emotions in schizophrenia, rather than a reduced ability to process the spatial configuration features necessary for understanding emotions (Caruana et al., 2020; Pinkham et al., 2003, 2011, 2016; Seymour et al., 2016).

Here, we try to shed some light on gaze perception with and without emotion in 22q11.2 children. To do this, we proposed a task in which children were presented with a behavioral *oddball* paradigm with three types of stimuli: geometrical figure, gaze, and emotional gaze. For each type of stimuli, two conditions were proposed: rare stimuli among frequent stimuli. The participant had to press a response key for each stimulus as quickly as possible. In order to control anticipated responses and to assess inhibitory control over gaze, No-Go stimuli were added. According to the literature, rare stimuli in general decrement in performance compared to frequent stimuli (Huettel & McCarthy, 2004; Schlüter & Bermeitinger, 2017). If gaze and emotional gaze stimuli gain processing priority, performance should be better for these stimuli compared to geometrical figure stimuli, regardless of participant group. On the other hand, if the gaze is correctly processed in the 22q11.2DS, similar results between the groups should be observed. On the other hand, if, the slightest exploration of the eye contour found in the literature is a sign of avoidance/misinterpretation of specifically self-directed gaze, then children with 22q11.2DS should respond exacerbated (i.e., abnormally low proportions of correct responses) to gaze and emotional gaze stimuli.

## 2. Method

### 2.1 Participants

Twenty-three children with 22q11.2DS (mean age in years = 8.75, SD = 2.25) and thirty-three healthy controls (mean age in years = 8.5, SD = 2.52) took part in the study[2]. The two groups (controls and 22q11.2 children) were matched in age and gender. All children were recruited through the Center of Rare Diseases Reference, GénoPsy, in Lyon (France). Participants with the following criteria were excluded from the study: (i) difficulties in understanding or lack of command of the French language, (ii) significant comorbid medical conditions, such as the presence or history of neurological disorders affecting the cerebral function, (iii) presence of a severe visual or hearing impairment interfering with the assessment. The diagnosis of 22q11.2DS was confirmed in all patients by fluorescence in situ hybridization (FISH) and complete genomic hybridization (CHG-Array). Each parent and children signed an informed consent and the study was approved by a national Ethics Committee (CPP Est-II, No. 2020-A01370-39; NCT04639388).

### 2.2 Stimuli

Three types of stimuli named target stimulus were created using GIMP version 2.10 software: (i) geometrical figures (rectangles) occupying an angular space of 6.7° x 2° drawn in black (mean luminance of 5 measures = 0.21 cd/m$^2$, SD = 0.03) presented on a gray background (mean luminance of 5 measures = 156.24 cd/m$^2$, SD = 2.17) including in the center either left-pointing or right-pointing triangles (frequent stimulus), or diamonds (rare stimulus); (ii) gaze occupying an angular space of 7.8° x 2.4° (width × height) expressing no emotion, and with the pupils either looking to the right or left (frequent stimulus) (averted gaze luminance for the sclera (white) = 136.31 (±4.95) cd/m$^2$ ; averted gaze luminance for the pupil (black) = 34.19 (±7.70) cd/m$^2$), or directly at the participant (rare stimulus) (direct gaze luminance for the sclera

[2] In view of the small sample, it was not possible to subdivide the group of 22q11.2 children according to the presence or absence of psychotic symptoms.

(white) = 104.1 (±5.43) cd/$m^2$ ; direct gaze luminance for pupil (black) = 21.57 (±8.75) cd/$m^2$; (iii) emotional gaze occupying an angular space of 7.8° x 2.4° (width × height) looking directly at the participant, and expressing either no emotion (frequent stimulus) or expressing an emotion (anger or sadness; rare stimulus). No-Go stimuli were created by adding an oval around the eyes for gaze and emotional gaze conditions (10.3° x 14°) and a rectangle (10.7° x 15°) around the geometrical figure. Finally, two types of predisplay stimuli were created: (i) closed eyes for gaze and emotional gaze conditions and (ii) empty geometrical figure for geometrical figure condition. The stimuli were presented in the center of the screen and covered an angular space of 7.8° x 2.4° at a viewing distance of 40cm. The angular distance between the two eyes (center to center) was 3.3° and the angular distance between the fixation cross and the center of each eye was 2.7°. The fixation cross was presented in the center of the screen and measured 1.4° x 1.4°. All instructions and stimuli were presented on a 15-inch screen, with a resolution of 1920x1080 pixels. Stimulus presentation, timing and data collection were controlled by OpenSesame (Mathôt et al., 2012). The experiment was conducted on a DELL computer equipped with an *Intel® UHD Graphics 620* card and took place in a normally lit and quiet room.

### 2.3 Procedure

The three types of stimuli (geometrical figures, gaze and emotional gaze) determined three blocks presented in Latin Square across the participants. In each block, frequent stimuli occurred at a frequency of 80%, rare 10%, No-Go 10%. In the geometrical figure and gaze block, the occurrence of frequent stimuli (right/left) was equiprobable. Each participant completed 80 trials per frequent condition, 10 trials per rare condition and 10 trials per No-Go condition. In the emotional gaze block, the occurrence of rare stimuli (anger/sadness) was also

equally probable. Each participant completed 160 trials per frequent condition, 20 trials per rare condition and 20 trials per No-Go condition. These factors were controlled. Each block began with the presentation of a fixation cross in the center of the screen during 1500ms. Each trial began with the presentation of the predisplay stimulus for 750ms and it was followed by a target stimulus (frequent, rare) until the participant's response, or a No-Go stimulus for 1000ms. On each trial, the stimulus condition (rare target, frequent target, No-Go) was chosen randomly by the computer (see Figure 1). The participants were told that they would see eyes or geometrical figures appear on the screen. They were asked to press the spacebar as quickly as possible as soon as the eyes opened or the geometrical figures were filled with triangles or diamonds, and to withhold from pressing if the stimuli were surrounded by a large circle (gaze and emotional gaze conditions) or a large rectangle (geometrical figures condition). Once the participant had heard and understood the instructions, the experiment could begin. The examiner could press any key to start. The block with the gaze and geometrical figures stimuli lasted approximatively 5 minutes and the one with the emotional gaze stimuli, 10 minutes. Correct responses were recorded by the computer program. At the end of the experiment (which lasted about 20 minutes), a screen was displayed to thank the participants and tell them that the experiment was over. The participants were then debriefed. No training session was conducted.

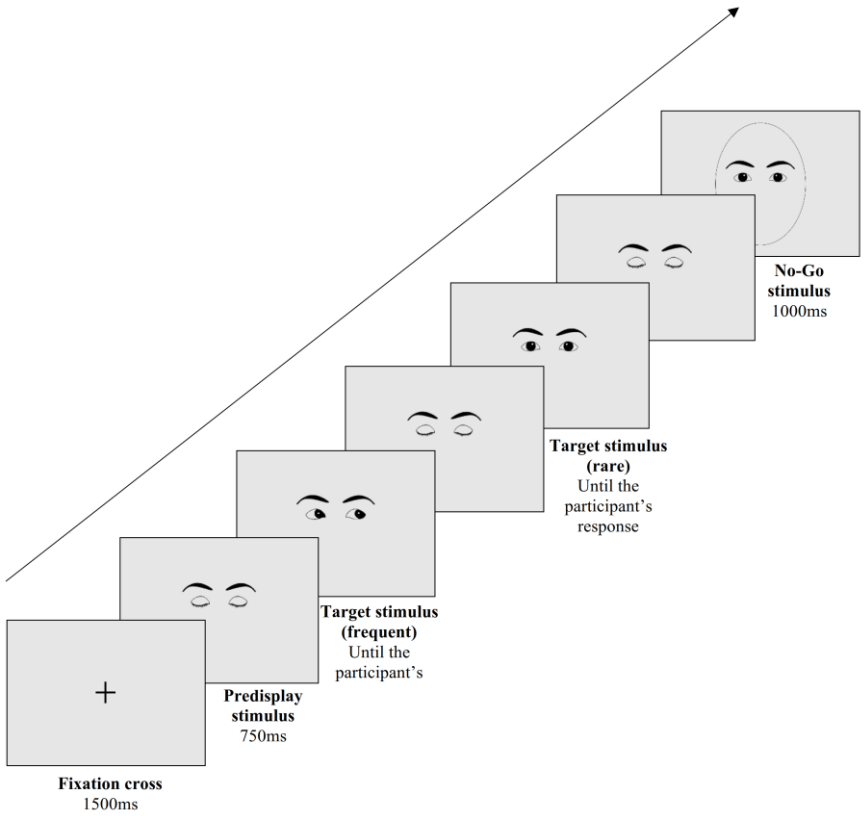


Fig 1. Illustration of experimental stimuli and procedure for the gaze block.

The stimulus condition (rare target, frequent target, No-Go) was chosen randomly by the computer. Correct responses were recorded by the computer program.

### 2.4 Design and analysis

Statistical analyses on demographic characteristics were performed with a non-parametric independent test (Mann-Whitney) and the Chi square test ($\chi^2$). The response times could not be analysed due to their excessive heterogeneity. The proportion of correct responses on the three types of stimuli was analysed through a mixed analysis of variance (ANOVAs, $\alpha$ = .05, throughout) with the type of stimulus (geometrical figure, gaze and emotional gaze) and condition of stimulus (rare and frequent) as within-participants factors, and the group (controls, 22q11.2 children) as between-participants factor. The proportion of No-Go correct responses on the three types of stimuli was analysed through a mixed analysis of variance (ANOVAs, $\alpha$

= .05, throughout) with the type of stimulus (geometrical figure, gaze and emotional gaze) as within-participants factors, and the group (controls, 22q11.2 children) as between-participants factor. Finally, in order to study behavioural responses related to inhibition capacities, we calculated a precision index from the stimulus Go-rare and No-Go-rare by subtracting the false alarm (1-(No-Go-rare)) to the hit (Go-rare). The Greenhouse–Geisser sphericity correction was applied whenever necessary. Partial eta-squared ($\eta^2_p$) coefficients were used to express effect sizes. Multiple post-hoc comparisons were conducted using the Holm test. Statistics were computed using JASP (JASP Team, 2022).

## 3. Results

Four children with 22q11.2DS and one healthy control could not perform the entire experimental task, leaving nineteen children with with 22q11.2DS (mean age in years = 9.05, SD = 2.28) and thirty-two healthy controls (mean age in years = 8.64, SD = 2.44) were included in the data.

### 3.1 Participants' characteristics

No difference was found in age ($U$ = 336, $p$ = .54). No group difference was found in terms of the percentages of boys and girls ($\chi^2(1) = 0.95$, $p$ = .33). These demographic characteristics are presented in Table *1*.

### 3.2 Eye direction perception and emotional gaze perception

As the proportion of correct responses was concerned, the main effect of group was revealed to be significant [F(1,49) = 9, $p$ = .004, $\eta^2_p$=.16], with the overall proportion of correct responses being lower for 22q11.2 children (mean = 0.78, SD = 0.17) than for the controls (mean = 0.88, SD = 0.13). The main effect of the type of stimulus was not significant [F(2,98) = 2.3, $p$ = .11, $\eta^2_p$=.05].

A significant group*condition of stimulus was observed, $F$(1,49) = 9.06, $p$ < .05, $\eta^2_p$=.16. *Post-hoc* analyses showed that for frequent stimuli, no significant difference was observed between the two groups (22q11.2 children: mean = 0.81, SD = 0.17; controls: mean = 0.88, SD = 0.12), whereas, for rare stimuli, the proportion of correct responses was lower in the 22q11.2 children group (mean = 0.76, SD = 0.18) than the control group (mean = 0.88, SD = 0.13) ($p$ < .05).

A significant group*types of stimuli*condition of stimuli interaction effect was observed, $F$(2,98) = 3.21, $p$ < .05, $\eta^2_p$=.06. Partial analyses of variance were conducted on each condition of stimulus. For the frequent stimuli, the group*type of stimulus was not significant [$F$(1,81) = 1.56, $p$ = .22, $\eta^2_p$ = .03]. For the rare stimuli, a trend effect of the group*type of stimulus was observed [$F$(1,92) = 2.7, $p$ = .08, $\eta^2_p$ = .05]. For emotional gaze stimulus, 22q11.2 children scored significantly lower (mean = 0.69, SD = 0.17) than controls (mean = 0.88, SD = 0.13) ($p$ < .001). Moreover, while the scores of the control participants were substantially identical for the three types of stimuli, 22q11.2 children had significantly poorer performance for the emotional gaze stimuli (mean = 0.69, SD = 0.17) compared to the gaze stimuli (mean = 0.82, SD = 0.14) ($p$ < .001) (see Figure 2).

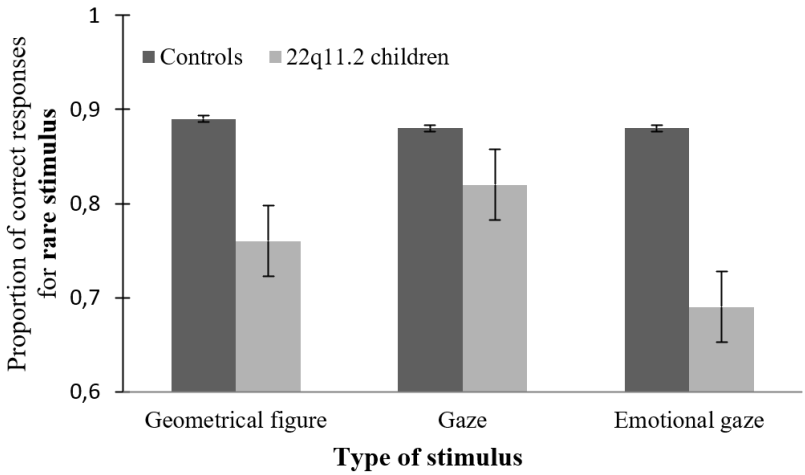


Fig 2. Mean proportion (±1 standard error of the mean) of correct responses for rare stimulus given by 22q11.2DS patients and controls in three types of stimuli evaluating gaze perception with and without emotion.

As far as the proportion of correct responses for No-Go stimuli was concerned, the main effect of group was revealed to be significant [$F(1,49) = 5.9$, $p < .05$, $\eta^2_p = .11$], with the overall proportion of correct responses being lower for 22q11.2 children (mean = 0.8, SD = 0.14) than for the controls (mean = 0.87, SD = 0.14). Moreover, the main effect of the type of stimulus was revealed to be significant [$F(2,98) = 11.66$, $p < .001$, $\eta^2_p = .19$]. The proportion of correct responses for No-Go stimuli was significant higher for gaze stimuli (mean = 0.9, SD = 0.11) compared to geometrical figures stimuli (mean = 0.83, SD = 0.15), and was significant lower for emotional gaze stimuli (mean = 0.78, SD = 0.15) compared to geometrical figures and gaze stimuli.

As far as the response precision was concerned, the main effect of group was revealed to be significant [$F(1,49) = 13.53$, $p < .001$, $\eta^2_p = .22$], with higher response precision for controls than 22q11.2 children. Moreover, the main effect of type of stimulus was revealed to be significant [$F(2,98) = 8.98$, $p < .001$, $\eta^2_p = .16$], with higher precision for gaze stimuli than for geometric

figure stimuli, and lower accuracy for emotional gaze stimuli compared to the other two (geometrical figure and gaze stimuli). A trend effect of the group*type of stimulus was observed [$F(2,98) = 2.56$, $p = .08$, $\eta^2_p = .05$]. Post hoc analyses showed that for emotional gaze stimulus, 22q11.2 children were significantly less accurate than controls ($p < .001$). Moreover, while no significant difference was found in the control group between each type of stimulus, 22q11.2 children were significantly less accurate for emotional gaze stimulus than gaze stimulus ($p < .001$) (see Figure 3).

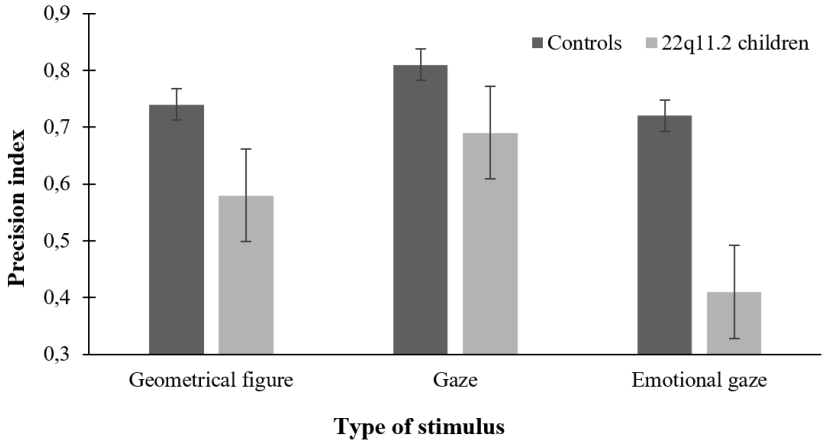


Fig 3. Precision index (±1 standard error of the mean) from the stimulus Go-rare and No-Go-rare calculated for 22q11.2DS patients and controls in three types of stimuli evaluating gaze perception with and without emotion.

## 4. Discussion

This study aimed at investigating gaze perception with and without emotion in a sample of children with 22q11.2DS at genetic risk for psychosis compared to neurotypical children (Lattanzi et al., 2018; Tang et al., 2017). For this, we proposed a task in which children were presented with a behavioral *oddball* paradigm with three types of stimuli (geometrical figures,

gaze, and emotional gaze) and for each type of stimuli, two conditions were proposed: rare stimuli and frequent stimuli. For the geometrical figure type of stimulus, the frequent stimuli were consisted in rectangles including in the center triangles pointing to the left or to the right, and the rare stimuli, rectangles including diamonds. For the gaze type of stimulus, the frequent stimuli were consisted in gaze expressing no emotion, and with pupils looking to the right or left, and the rare stimuli, neutral direct gaze. Finally, for the emotional gaze type of stimulus, the frequent stimuli were consisted in neutral direct gaze, and the rare stimuli, direct gaze expressing an emotion (anger or sadness). The participant had to press a response key for each stimulus as quickly as possible. In order to control anticipated responses and to assess inhibitory control over gaze, NoGo stimuli were added. We will discuss the results of interest.

The main effect of the type of stimulus (geometrical figure, gaze and emotional gaze) was not significant. Our hypothesis that performance should be better for gaze and emotional gaze stimuli compared to geometrical figure stimuli, regardless of participant group, because a processing priority is not validated. This lack of results may reflect a lack of sensitivity of the experiment.

On the other hand, we hypothesized that if the slightest exploration of the eye contour found in the literature is a sign of avoidance/misinterpretation of specifically self-directed gaze (Zaharia et al., 2018), children with 22q11.2DS should respond exacerbated (i.e., abnormally low proportions of correct responses) to gaze and emotional gaze stimuli. Our results show that, children with 22q11.2DS presented significant lower proportion of correct responses than controls only for the rare stimuli and regardless of type of stimulus (geometrical figure, gaze and emotional gaze). The detection of a rare stimulus leads to attentional capture causing a decrement in performance (Huettel & McCarthy, 2004; Schlüter & Bermeitinger, 2017). Our

results show that 22q11.2 children have lower performance for rare stimuli compared to neurotypical children, which goes in the direction of a more marked attentional capture, regardless of the nature of the target presented (Linton et al., 2021). However, our results also support a more specific effect of emotion, probably through attentional capture. Indeed, the effect explained above seems to be mainly due to rare stimuli of the emotional gaze type. Thus, the fact of seeing a negative emotion, anger or sadness, would lead to a greater attentional capture and, probably to a more difficult subsequent attentional disengagement (Kalanthroff et al., 2017). This would decrease performance. Complementarily and interestingly, when we are interested in rare stimuli, 22q11.2 children did not behave in the same way whether they were confronted with a neutral direct gaze (in the gaze type of stimulus) and with a negative emotional direct gaze (in the emotional gaze type of stimulus). The schizophrenia literature tells us that people with active paranoid delusions over-attribute threat to emotional stimuli (Pinkham et al., 2011, 2016). The stimuli presented here combining anger and sadness, it may be hypothesized that the effect of emotion is linked to an over-interpretation of anger in 22q11.2 children. This is probably in relation to their risk of developing psychotic symptoms like paranoia (Babinet et al., submitted). Indeed, paranoid symptomatology is a common feature found in people with 22q11.2DS (Schneider et al., 2017). Since the recognition of anger can be linked to a perception of a threat when the gaze is directed towards us (Cushing et al., 2018; Whalen et al., 2001), it is likely that the paranoid symptomatology accentuates this feeling of threat in 22q11.2 population.

On the other hand, our results suggest that 22q11.2 children have more difficulty globally in inhibiting their behavioral response (lower proportion of correct No-Go responses), which is in line with the inhibition deficit reported in the literature (Kates et al., 2015). Furthermore, the significant effect of the type of stimuli supports the idea that the processing of a neutral direct

gaze and an emotional direct gaze is different (Itier & Batty, 2009). This difference may be explained by the concept of approach/avoidance resulting in distinct inhibitory control (Hietanen, 2018). That our results indicate a larger effect of emotion in 22q11.2 children may be explained by the impaired development of response inhibition in 22q11.2DS children (Francisco et al., 2020; Shapiro et al., 2014). If the perception of an emotion is associated with a stronger threat in 22q11.2DS, the difficulties of inhibition would be linked to a threat attribution bias rather than to poor recognition of the emotion (Caruana et al., 2020).

Our study has some limitations that should be highlighted. First, the type of stimulus used here, namely the sketch of a gaze, does not resemble real stimuli (such as photographs). Nevertheless, one of reasons for this choice was to optimize our control of all aspects of the stimuli and avoid the typical problems that natural stimuli give rise to (i.e., contrast, saliency, visual complexity). Moreover, the use of drawings minimizes confounds related to facial characteristics that are present in natural photographs, i.e., gender, age, attractiveness, and ethnicity. Another limitation concerns the size of the group of 22q11.2 children and the lack of assessment of the impact of potential paranoid symptoms on behavior. Several studies suggest a link between paranoid symptoms, emotion recognition and inhibitory control (Caruana et al., 2020; Francisco et al., 2020; Schneider et al., 2017). It would therefore be interesting to complete the sample of the 22q11.2DS group and to be able to measure paranoid or even psychotic symptoms more generally.

## 5. Conclusions

To conclude, our study provides new insights into the gaze perception with and without emotion in 22q11.2DS. It appears that the eyes are a special cue but that the atypical processing of the information conveyed comes mainly from an effect of the emotion associated with the gaze. Inhibitory capacities seem to be an important marker associated to emotional salience and could be linked to the presence of psychotic symptoms in 22q11.2DS but also in the general population (Francisco et al., 2020).

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**Declarations of interest**

None

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Table 1. Descriptive statistics for age and gender for each experimental group.

| **Variable** | **22q11.2 children (n = 19)** | **Controls (n = 32)** | **Group differences** |
|---|---|---|---|
| **Ratio Female / Male** | 8/11 | 18/14 | $X^2(1) = 0.95$, $p = .33$ |
| **Mean (SD) Age in years** | 9.05 (2.28) | 8.64 (2.44) | $U = 336$, $p = .54$ |

# CHAPITRE 3

## Le traitement des émotions faciales

## Le traitement des émotions faciales dans les maladies rares : l'exemple du 22q11.2DS

La région de l'œil a, comme nous l'avons vu, un rôle fondamental dans l'indication de la direction du regard d'autrui, sur ses intentions mais également dans la reconnaissance des émotions. L'étude des émotions est maintenant une question classique en sciences cognitives et en neuropsychologie expérimentale. La majorité des études s'intéresse aux relations entre les émotions et la cognition (Sander & Scherer, 2009), et d'autres examinent l'origine et le développement des émotions (Ekman & Friesen, 1971, 1978). L'étude des expressions faciales émotionnelles est déterminante puisqu'il s'agit d'indices sociaux nécessaires à la communication interpersonnelle, au même titre que les indices émotionnels prosodiques (Adolphs, 2002), et l'attention conjointe par l'orientation du regard ou par le pointage (Hood et al., 2003). Depuis la fin des années 1970, les psychologues ont étudié le développement de la discrimination des expressions faciales émotionnelles car, si comme le suggère Ekman (1993) certaines expressions sont universelles et ne sont pas le fruit d'un apprentissage, il est possible qu'elles soient perçues dès le début de la vie, et qu'elles aient un caractère innée. Cette hypothèse est particulièrement intéressante puisqu'elle implique que la capacité de perception des expressions faciales soit très précoce, et qu'elle ne résulte pas uniquement des capacités de socialisation. De nombreuses études se sont donc intéressées au développement normal de la perception des émotions (Bayet et al., 2014). Il apparaît ainsi que dès les premiers mois de vie, les nourrissons sont capables de percevoir un changement d'expression faciale, et sont également plus attirés par les visages exprimant la joie. Petit à petit lors des premiers mois de vie, les nouveau-nés vont être capables de distinguer différentes émotions entre elles (Bornstein & Arterberry, 2003; Kuchuk et al., 1986; LaBarbera et al., 1976; Wilcox & Clayton, 1968). Le développement de la reconnaissance des émotions, autrement dit la capacité à labéliser les émotions, se fait dans les premières années de vie (Widen & Russell, 2003). Compte tenu de l'importance de la perception des émotions faciales, on s'attend à ce que toute perturbation de la capacité à détecter ou à interpréter les émotions soit susceptible d'altérer les comportements sociaux. Des études dans le domaine du développement de la cognition sociale et ses troubles (par exemple, le trouble du spectre de l'autisme, la schizophrénie) renforcent cette idée ainsi que l'intérêt de mieux comprendre la perception de ces expressions (Collin et al., 2013; Corbett et al., 2009; Landowska et al., 2022). Dans la lignée des études sur le Trouble du Spectre de

l'Autisme, d'autres chercheurs se sont intéressés à un autre trouble du neurodéveloppement, le 22q11.2DS. La littérature expose de manière assez claire des difficultés dans le champ des cognitions sociales, et plus particulièrement dans la reconnaissance des émotions faciales, chez les enfants et adultes porteurs d'un 22q11.2DS (Campbell et al., 2015; Leleu et al., 2016). Toutefois, les études portent généralement sur la labélisation de l'émotion faciale (Campbell et al., 2010) ou l'attribution de représentations mentales (Jalbrzikowski et al., 2012). Peu d'études se sont intéressées à l'attribution d'émotions dans un contexte social (Campbell et al., 2015) ou bien à la prosodie émotionnelle (Shashi et al., 2012).

L'étude 4 a pour objectif de préciser chez les enfants porteurs d'un 22q11.2DS les déficits de reconnaissance des émotions faciales tant lorsqu'on présente un visage seul, qu'en contexte social ou à travers la voix (prosodie). Pour cela, un protocole composé de trois tâches expérimentales : (i) une tâche de reconnaissance des expressions faciales, (ii) une tâche d'attribution de l'émotion à un personnage dans un contexte social et (iii) une tâche d'attribution de l'émotion à travers la voix en utilisant des dialogues, a été proposé aux enfants.

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ORIGINAL CONTRIBUTION

# What do error patterns in processing facial expressions, social interaction scenes and vocal prosody tell us about the way social cognition works in children with 22q11.2DS?

**Elodie Peyroux[1,2] · Marie-Noëlle Babinet[1,2] · Costanza Cannarsa[1,2,3,4] · Charline Madelaine[3,4,5] · Emilie Favre[1,2] · Caroline Demily[1,2] · George A. Michael[3,4]**

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## Abstract

Impairments in social cognition have been frequently described in 22q11.2 deletion syndrome (22q11.2DS) and are thought to be a hallmark of difficulties in social interactions. The present study addresses aspects that are critical for everyday social cognitive functioning but have received little attention so far. Sixteen children with 22q11.2DS and 22 controls completed 1 task of facial expression recognition, 1 task of attribution of facial expressions to faceless characters involved in visually presented social interactions, and 1 task of attribution of facial expressions to characters involved in aurally presented dialogues. All three tasks have in common to involve processing of emotions. All participants also completed two tasks of attention and two tasks of visual spatial perception, and their parents completed some scales regarding behavioural problems of their children. Patients performed worse than controls in all three tasks of emotion processing, and even worse in the second and third tasks. However, they performed above chance level in all three tasks, and the results were independent of IQ, age and gender. The analysis of error patterns suggests that patients tend to coarsely categorize situations as either attractive or repulsive and also that they have difficulties in differentiating emotions that are associated with threats. An isolated association between the tasks of emotion and behaviour was found, showing that the more frequently patients with 22q11.2DS perceive happiness where there is not, the less they exhibit aggressive behaviour.

**Keywords** 22q11.2 Deletion syndrome · Emotional processes · Theory of mind · Velo-cardio-facial syndrome · Social cognition

## Introduction

It is now well documented that children and adults with 22q11.2 deletion syndrome (22q11.2DS) have poorer social competences, including mood lability, shyness, and difficulties in initiating and maintaining social relationships, compared with typically developing young people [1]. In 22q11.2DS, these social dysfunctions could be partly underlain by impairments in social cognitive processes (for a review, see [2]) and could also be linked to the emergence of psychosis [3]. Social cognition, which is defined as the ability to understand oneself and others in the social world [4], consists of emotional processing, theory of mind (ToM), attribution style, and social perception and knowledge [5]. The present study addresses three components of social cognition: (i) the identification of facial expressions, which has been extensively investigated in 22q11.2DS populations and yet provided inconsistent results, and two elements that are

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✉ George A. Michael
george.michael@univ-lyon2.fr

1 GénoPsy, Reference Center for Rare Diseases, Le Vinatier Hospital, 95 Bd Pinel, Bron, France

2 EDRPsy, UMR 5229, CNRS, 67 Bd Pinel, Bron, France

3 Université de Lyon, Lyon, France

4 Laboratoire D'Étude Des Mécanismes Cognitifs (EA 3082), Université Lumière Lyon 2, Lyon, France

5 Laboratoire de Psychologie de Caen Normandie PALM (EA 7452), Université Caen-Normandie, Caen, France

critical for everyday social cognitive functioning but have received extremely little attention in the literature, namely (ii) the comprehension and interpretation of visual scenes involving emotions and (iii) the identification of prosodic aspects of dialogues.

Concerning recognition of emotional facial expressions, despite frequent reports of social competences, several studies have failed to document examples other than a general impairment in 22q11.2DS [1, 6, 7], even though various and inconsistent deficits have been highlighted in the literature. Indeed, according to some authors, patients with 22q11.2DS have difficulties in recognizing facial expressions of fear, anger and disgust, while recognition of happiness, sadness and surprise may be efficient [8]. However, others have reported different results [3]. It has been suggested that such an impairment might be due to slowed, insufficient or inefficient gathering and processing of information. For instance, Franchini et al. [9] suggested that patients need more time to recognize emotions than healthy controls do, whereas using a morphing continuum, another study found that 22q11.2DS patients require higher intensities of emotion to accurately recognize facial expressions [7]. Conversely, patients with 22q11.2DS were found to exhibit fewer fixations on relevant facial features such as the eyes, the nose and the mouth [8, 10, 11], and such atypical and inefficient visual scanpath patterns could partially explain the poorer emotion identification skills. According to Campbell et al. [8], patients spent less time than controls looking at the eye region, which is known to be an important region for accurate emotion recognition, and spent more time looking at the mouth [10, 12]. Finally, in 22q11.2DS, impairments in emotional facial processing may be underlain by lower level visual and attentional impairments that could play a central role in the difficulties observed in these social cognitive skills [13].

Processing and understanding social information also requires collecting and processing cues beyond facial expressions, such as postural and vocal information that is present in social interactions or prosody. In most cases, the experimental tasks that have been used to study emotion recognition in 22q11.2DS have been based on emotional labelling of people depicted in photos [8] or in representations of a cognitive mental state described in vignettes [3]. Little has been done to investigate the understanding of more common social contexts, and when it has been done, it proved difficult to disentangle the social cognitive difficulties from executive deficits [1]. Concerning emotional prosody, only one study has compared the performance of patients with 22q11.2DS to that of healthy controls [14], and it failed to find any difference between these groups in the way they perceive and understand vocal emotions. In sum, contrary to the recognition of facial expressions, which has been extensively investigated, very little has been done regarding the interpretation and understanding of situations or social and environmental contexts, and almost nothing has been done to explore the recognition and interpretation of vocal prosody. However, real-life social events are not composed solely of facial expressions but are mostly made of complex interactions through which postures, attitudes and voices have to be interpreted. The way patients with 22q11.2DS comprehend scenes and vocal prosody has yet to be understood.

The existing studies regularly contradict each other. This might be due either to the variety of stimuli and paradigms used to assess the different facets of social cognition. But it also might also be due to the fact that it is rather uncommon that the same participants complete various tasks using similar stimuli and similar procedures. Another potential source of inconsistency might be the fact that some studies have focused only on children, others focused on adults, and some included both children and adults. Finally, most studies included patients with IQ levels lower than the normal range and failed to tease apart the effects of global cognitive deficits from impairments in social cognition. Here, we aimed to compare the performance of children with 22q11.2DS to that of controls on three tasks assessing emotional aspects of social cognition. Even though non-naturalistic stimuli were used, they were created to render the tasks comparable and, therefore, allow distinguishing the components of social cognition. The first task assessed the recognition of isolated emotional facial expressions (facial expression recognition task). The second task assessed the attribution of facial expressions to faceless characters involved in visually presented social interactions (face-cartoon-matching task). This task involved the emotional dimension of theory of mind (ToM), also called affective ToM [15], which is the ability to understand that other people have mental states that are independent from one's own [16]. The third task assessed the attribution of facial expressions to characters involved in aurally presented dialogues (face-prosody-matching task). Investigating the performance of the same participants across all three aspects of social cognition is critical for comprehending social cognitive processes in a more global way. In fact, all three tasks used here involve some common processes (i.e. identification of an emotion, visual search for the right face and choosing it), and each task also involves some specific processes (e.g. taking into account visual or auditory cues, interpretation of the whole context, etc.). Therefore, comparison of the three tasks within each group leads to understand what determines performance. This is why all stimuli were specifically designed for the present study to enable the comparison of the three.

In addition to the analysis of correct performances, which could provide insight into what might not work correctly in 22q11.2DS patients' recognition of facial expressions and an understanding of visual social contexts and vocal prosody, as well as the extent of such difficulties, we also aimed to analyze the confusion among the emotions in each task

to unravel the way 22q11.2DS patients process emotional information to understand social contexts. The analysis of error patterns in 22q11.2DS patients, compared to controls, is even more important, as the literature is quite inconsistent on this issue. Understanding confusions between emotions in each task could provide some hypotheses about the origins of impairments in social cognition. For instance, regular confusion between two emotions in the facial expression recognition task might reveal that the parts of the faces that individuate emotions are less attended to and that scanning of some kinds of expressive faces might be incomplete [8]. On the other hand, regular confusion among emotions in the face-cartoon-matching task might reveal the existence of biases in comprehending the nature of the situations depicted [17], biases in interpreting social and environmental contexts [18] and even that some situations might regularly be appraised as a mixture of different emotions. Finally, regular confusion among emotions in the face-prosody-matching task might reveal difficulties in the perception and interpretation of vocal parameters that differentiate emotions [19]. Unfortunately, although we predicted that patients with 22q11.2DS would perform more poorly than controls in all three tasks, the scarcity of the data available in the literature, as well as the abovementioned inconsistencies, did not allow us to anticipate specific error patterns.

Simultaneously to the three social cognitive tasks, an assessment of visual spatial attention and perception abilities, as well as scanning and exploring competencies was proposed. According to some authors, these cognitive functions could underlie difficulties in emotional processing [8, 9, 12, 13]. Thus, we assumed that results obtained in the social cognitive tasks could be partly explained by measures of attention and visual spatial abilities. We also assessed several components of behaviour through parent-completed scales, more specifically irritability, agitation and crying; lethargy/social withdrawal; stereotypic behaviour; hyperactivity/noncompliance; and inappropriate speech, but also aggressive behaviour and self-esteem. The aim was to measure the impact of social cognitive impairments on children with 22q11.2DS's behaviour. Social cognition appears to have a direct and strong impact on everyday life functioning in people with schizophrenia [20–22], but this relation is still poorly understood in people with 22q11.2DS. Indeed, social cognitive impairments have been extensively studied in relationship with the emergence of psychotic symptoms in adults [3], yet, little is known about the impact of social cognition on specific behaviour in children and adolescents with 22q11.2DS [23]. For instance, in a cross-sectional study, an association was observed between social cognitive measures and a behavioural screening questionnaire completed by parents [6]. However, another research failed to evidence any correlation between social cognition and behaviour [14]. These discrepancies may be due to methodological differences between the studies, but also due to the sensitivity of the variables used to assess cognition, social cognitive function and behaviour. It is, therefore, difficult to predict with precision whether such association would be found or not in children with 22q11.2DS, yet what was reported in adults may allow us to expect that social cognitive function will be associated with behaviour.

## Methods

### Participants

We conducted a power/sample size analysis. Based on ten studies that are cited in the introduction section of this paper, the average and sample-weighted effect size of the most prominent and frequently reported difference in social cognition between controls and 22q11.2DS patients, i.e. overall accuracy in facial expression recognition (apprehension of social contexts and perception of prosody were only rarely studied and it is not possible to conduct specific power/sample analyses on already published data) is $d^* = 1.058$. Provided a power of 80% to detect such an effect, the total sample size needed is 32 individuals, combining controls and patients.

Sixteen children with 22q11.2DS and 22 healthy controls aged 5–13 years took part in the study. The two groups were matched in age and gender. Participants with difficulties in comprehension of the French language and/or with significant comorbid medical conditions, such as the presence or history of neurological disorders affecting the brain function, presence of severe visual or hearing impairment interfering with assessment, absence of French language proficiency or important reading difficulties, were excluded from the study.

The diagnosis of 22q11.2DS was confirmed in all patients by fluorescence in situ hybridization (FISH) and complete genomic hybridization (CHG-Array). To be included, participants with 22q11.2DS had to have an IQ in the normal range of 70–130 (assessed with Raven's Coloured Progressive Matrices) [24]; this is a non-verbal test of fluid intelligence, all the items of which consist of visual geometric designs with a missing part. The participant is given six choices to pick from and fill in the missing part) and a normal ear, nose, and throat (ENT) examination.

### Cognitive testing

Except from the above-mentioned evaluation of the IQ level, a short cognitive assessment was also conducted. This included two tests of visual spatial attention/scanning and exploring: (i) the Sky Search subtest from the Test of Everyday Attention for Children (TEA-Ch) assessing selective/focused attention [25], and (ii) the Overlapping lines task

[26] assessing visual spatial scanning and control of oculomotor behaviour. The cognitive assessment also included two tests of visual spatial perception taken from the A Developmental NeuroPsychological Assessment battery (NEPSY-II) [27, 28]: (i) the arrows subtest assesses the ability to judge directionality, and (ii) the orientation subtests assesses the perception of visual spatial relations and positions. The choice of attention/scanning and visual spatial perception was made on the basis of previous findings suggesting that these functions may explain at least partly the performance of perception of facial expressions in 22q11.2DS [8, 9, 12, 13]. The proportion of errors was preferred to the proportion of correct responses (even if they reflect exactly the same thing) to have an overall coherent assessment with increasing scores denoting greater difficulty.

Please see Supplementary Material for a detailed description of the four tests.

## Assessment of behaviour

Behaviour was assessed through three parent-completed scales: (i) aberrant behaviours were assessed with the The Aberrant Behavior Checklist (ABC-C) [29], a 58-item questionnaire assessing on a four-point scale (0 = it is not a problem; 3 = it is a very important problem) the following behaviours: irritability, agitation and crying; lethargy/social withdrawal; stereotypic behaviour; hyperactivity/noncompliance; and inappropriate speech. The larger the score, the more a behaviour is judged by parents as being problematic; (ii) aggressive behaviour was assessed with the reactive–proactive aggression questionnaire [30, 31], a 6-item questionnaire using a 5-point Likert scale (0 = never; 5 = almost always). The larger the score, the more aggressive the child is described by his/her parents; and (iii) self-esteem was assessed through the self-esteem true/false 8-item subscale of the MDI-C [32]. The larger the score is, the less the self-esteem.

## Social cognition assessment

Social cognitive processes were assessed with a protocol intended for children and were composed of three tasks. All details can be found in the Supplementary Material. Visual stimuli were produced by a graphic designer using Photoshop CS5 software on a Wacom Bamboo A5 graphic tablet. All stimuli were especially created for this study and were validated through a sample of adults (see Supplementary Material). The first reason was to control at best all aspects of stimuli and avoid typical problems that exist with natural stimuli, such as photographs. These problems involve contrast, saliency, visual and auditory complexity. The second reason was to make all three tasks directly comparable since the response mode and the stimuli used for the responses were strictly identical in all three tasks. The third reason was that it was impossible to create natural stimuli for the face-cartoon-matching task and also for the face-prosody-matching task. The last reason was that some studies [33, 34] showed that young children have more difficulties recognizing facial expressions on photographs than on drawings of faces. The use of drawings minimizes confounds related to facial characteristics that are present in natural photographs but irrelevant to the emotion. These include gender, age, attractiveness, and ethnicity, as well as physical characteristics such as wrinkles and freckles.

All participants were tested in a silent room.

## Facial expression recognition task

The aim of the first task was to assess the identification of isolated facial expressions. Six hairless and genderless cartoon faces expressing the six basic universal emotions were drawn with black ink according to the traits listed by Ekman and Friesen [35]. The emotions were happiness, surprise, sadness, anger, disgust and fear. The six faces were presented simultaneously on A4 landscape-oriented sheets of white paper in two rows of three faces each (Fig. 1). Five sheets (i.e. a total of 30 stimuli, with each expression being presented 5 times) were produced, and the spatial location of each facial expression changed from 1 sheet to the next. For each sheet, the participant was required to point to the face that looked happy, sad, disgusted, angry, surprised or fearful. After the final sheet, the examiner proceeded to point to and simultaneously name each one of the faces, even if all responses given by the participant were correct. This aimed to reinforce the identification of each facial expression for the subsequent tasks. The task lasted approximately 5 min.

## Face-cartoon-matching task

The aim of this task was to assess the ability to understand the context of visually presented scenes [17] involving one to three faceless characters in situations where emotions were expressed. The scenes were drawn with black ink on white A4 landscape-oriented sheets. The target character

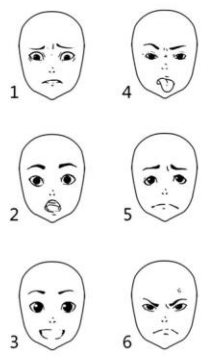


**Fig. 1** The six faces that were used in the facial expression recognition task. The same stimuli were also used in the face-cartoon- and the face-prosody-matching tasks as possible responses

was always wearing orange clothing to be immediately and easily detected and identifiable. The target character was a boy in half of the trials and a girl in the other half. Thirty scenarios were included in the test, depicting various everyday situations (see Supplementary Material for pilot testing and selection of stimuli). Each of the six facial expressions matched the emotion expressed by the target character, and for each expression, five scenarios were presented. A sixth scenario, which was associated with happiness, was used as both an example and a training trial. At the bottom of each scene, the six isolated facial expressions that were previously used were presented in a row that served as the answer choices (Fig. 2). The participant was required to point to the face the target character would make in each scene presented as quickly and as accurately as possible. The task lasted approximately 20 min.

## Face-prosody-matching task

The aim of this task was to assess the ability to understand the emotional context of aurally presented dialogues involving two characters. The dialogues always consisted of three sentences, the propositional content of which contained no emotion-related words (i.e. "first character: There are spoons on the table. Second character: three chairs are also there. First character again: and the window is open.") [36]. However, all three sentences were expressed with vocal emotion, and for each dialogue, the expressed vocal emotion was the same for all three sentences (e.g. all three sentences were expressed with anger). The dissociation between the propositional content and the emotional prosody aimed to drastically diminish any interference between the two. Thirty dialogues were created, 5 for each of the 6 basic emotions. A final dialogue (in which happiness was expressed) was created and used as an example and a training trial. The six isolated facial expressions used in the first test were used for the responses. They were presented on an A4 landscape-oriented white sheet, were placed on the table in front of the participant and were visible throughout the whole test. The participant was required to point to the face the characters would make in each dialogue. He/she was told to wait until the dialogue was over before giving an answer and to respond as accurately as possible. The task lasted less than 10 min.

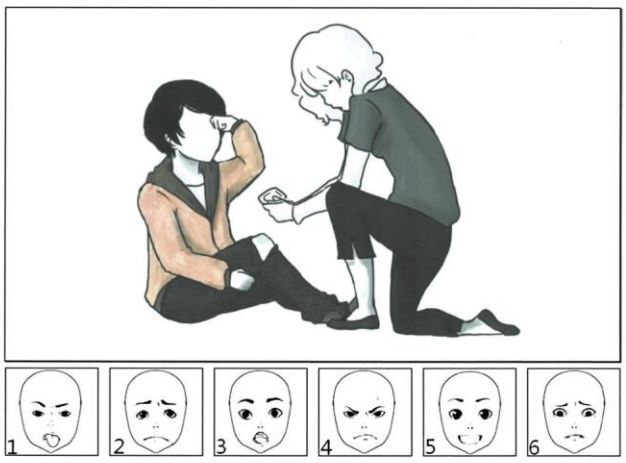


**Fig. 2** An example taken from the face-cartoon-matching task. At each new trial participants were requested to attentively look at the picture and choose among the six facial expressions depicted below the one that matched the best the face the unique character in orange clothing would make

## Statistical analyses

Several statistical analyses were conducted: (i) statistical analyses on demographic characteristics, IQ level, performance on cognitive tasks and behaviour were performed with Welch's $t$ test and the Chi square test ($\chi^2$). Cohen's $d$ was used to express effect sizes; it represents the difference between two means divided by a standard deviation for the data. (ii) Performance on the three tasks involving social cognitive processes was analyzed through a mixed analysis of variance performed on the proportion of correct responses. The Greenhouse–Geisser sphericity correction was applied. Partial eta-squared ($\eta^2_p$) coefficients were used to express effect sizes. Multiple comparisons were conducted with Bonferroni-corrected Welch's $t$ tests, and Cohen's $d$ was used to express effect sizes. (iii) The comparison of performance in these three tasks to chance level was conducted with Welch's $t$ tests, and Cohen's $d$ was used to express effect sizes. All three abovementioned statistical analyses were performed with JASP software, version 0.8.1.2 (JASP Team, 2017) and actual power—provided a power of 80% to detect the effect—was computed with the G*Power 3.1 freeware. (iv) The analysis of error patterns was conducted using resampling statistics. Due to the important number of expected response/given response possibilities in the analysis of errors ($N = 30$), the number of cells that could have contained values of 0 was very high. The assumptions of parametric tests were, therefore, difficult to meet, so we proceeded in the analysis of error patterns with the aid of resampling statistics [37]. Permutation tests were conducted, allowing the comparison of the error patterns of the patient and the control groups in each of the three tasks that assessed social cognition. The computation of the statistical probability was based on 5000 permutations for each task. These analyses were conducted with the Microsoft Excel (2011) software and a lab-made program. Permutation tests are robust and have many more advantages than just their good performance with data of the kind explored here. They give exact statistical significance directly from the data being analyzed, and all irregularities of the observed data are

maintained in the permuted datasets and are included in the estimation of the statistical probability. Of most interest is that they constitute powerful alternatives to more common corrections (e.g. Bonferroni procedures) for cases in which multiple comparisons are needed [38]. Since corrections are not needed, permutation tests are recommended in studies involving multiple statistical tests [39]. (v) Correlation analyses were conducted with the Spearman $\rho$ coefficient for each group independently. When a significant correlation was found in one group between the tasks of social cognition and the remaining cognitive tasks and behavioural scales, the assessment of differences in correlations between the two groups was conducted with the Steiger's test [40] to confirm or not that there is a group difference.

## Results

### Participants' characteristics

No difference was found in age. A marked difference was, however, found regarding the IQ levels with patients scoring lower than controls. Finally, no group difference was found in terms of the percentages of boys and girls, but boys outnumbered girls in both groups. These demographic characteristics are presented in Table 1.

### Cognitive testing

Patients had overall lower performance than controls in all cognitive tests. Indeed, as far as attention processes were concerned, patients made more errors than controls in the Sky search test of selective attention The proportion of errors was also greater for patients in the Overlapping lines test. As far as visual spatial perception was concerned, a similar pattern was found. The proportion of errors of patients was greater than that of the controls in the Arrows. The proportion of errors was also greater for patients in the Orientation test. These data are presented in Table 1.

### Parent-rated behaviour

Behavioural problems, as assessed through the ABC-C, were always more important for patients than controls. Indeed, such differences were found for irritability, agitation and crying, lethargy/social withdrawal, stereotypic behaviour, hyperactivity/noncompliance, and inappropriate speech. Furthermore, problems with Self-Esteem, as assessed through the MDI-C, were higher in patients than in controls However, aggressive behaviour was not found to be more frequent in patients ($M = 12.0$, SD = 4.9) than in controls. These data are presented in Table 1.

**Table 1** Demographic characteristics, performance in tests of cognition, and parent-rated behaviours of the two groups included in the present study

| | Controls | 22q11.2DS | *p* | Cohen's *d* |
|---|---|---|---|---|
| *N* | 22 | 16 | | |
| Girls (%) | 8 (36.4) | 6 (37.5) | | |
| Boys (%) | 14 (63.6) | 10 (62.5) | | |
| Age in years | 9.2 (2.5) | 8.1 (2.2) | 0.16 | 0.47 |
| IQ level | 111.3 (8.1) | 85.6 (12.9) | 0.001 | 2.44 |
| Attention/scanning | | | | |
| Sky search (TEA-Ch) | 5.7 (3.1) | 8.5 (4.3) | 0.039 | 0.73 |
| Overlapping lines | 0.15 (0.19) | 0.57 (0.41) | 0.001 | 1.28 |
| Visual spatial perception | | | | |
| Arrows (NePsy-II) | 0.23 (0.12) | 0.54 (0.20) | 0.001 | 1.84 |
| Orientation (NePsy-II) | 0.08 (0.13) | 0.61 (0.29) | 0.001 | 2.38 |
| Behaviour | | | | |
| Irritability, agitation and crying (ABC-C) | 1.3 (1.6) | 13.3 (9.9) | 0.001 | 1.68 |
| Lethargy/social withdrawal (ABC-C) | 0.3 (0.7) | 4.7 (3.2) | 0.001 | 1.90 |
| Stereotypic behaviour (ABC-C) | 0.13 (0.4) | 2.9 (3.8) | 0.009 | 1.05 |
| Hyperactivity/noncompliance (ABC-C) | 3.1 (3.9) | 12.1 (9.7) | 0.002 | 1.21 |
| Inappropriate speech (ABC-C) | 0.18 (0.5) | 2.56 (2.4) | 0.001 | 1.36 |
| Aggression | 10.4 (5.1) | 12.0 (4.9) | 0.32 | 0.33 |
| Self-esteem (MDI-C) | 0.50 (0.9) | 1.31 (1.3) | 0.034 | 0.76 |

## Comparison between the control and 22q11.2DS groups in tasks of social cognition

To examine the differences in the performance of the tests of emotional perception and social cognition, a mixed analysis of variance was performed on the proportion of correct responses, with the task (facial expression recognition, face-cartoon matching and face-prosody matching) and emotion (happiness, surprise, sadness, anger, fear and disgust) as within-subjects factors and the group (patients vs. controls) as the between-subjects factor. Since the IQ levels were found to be different between the two groups, since boys outnumbered girls in both groups, and since developmental changes may occur within the age range of our samples, IQ, age and gender were used as covariate values to control for their effects on performance. Here, we report only reliable effects that involved the group. The main effect of group was revealed to be significant [$F(1,33)=11.14$, $p=0.002$, $\eta^2_p=0.25$], with the overall proportion of correct responses being lower for the patients ($M=0.58$, SD = 0.14) than for the controls ($M=0.82$, SD = 0.1). Among the other effects, only the group × task interaction was revealed to be significant [$F(2,66)=3.40$, $p=0.044$, $\eta^2_p=0.09$; Fig. 3], with the IQ level, age and gender explaining as much as 8% of the variance altogether [without IQ, age and gender as covariates, the group × task interaction was $F(2,72)=7.1$, $p=0.002$, $\eta^2_p=0.17$]. Bonferroni-corrected multiple comparisons (cutoff level of significance $p=0.006$) revealed that patients scored lower than the controls in the facial expression recognition task [$t(36)=4.4$, $p=0.0001$, $d=1.48$; actual power 92.3%], the face-cartoon-matching task [$t(36)=4.15$, $p=0.0002$, $d=1.38$; actual power 89.6%], and the face-prosody-matching task [$t(36)=6.4$, $p=0.00001$, $d=2.14$; actual power 99.3%].

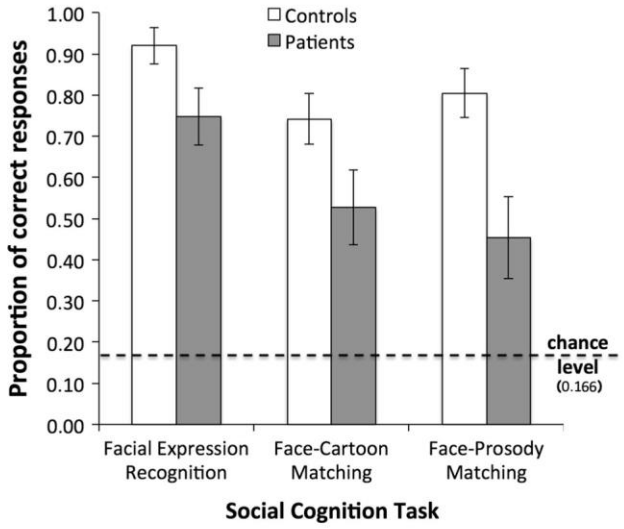


**Fig. 3** Mean proportion (±1 standard error of the mean) of correct responses given by 22q11.2DS patients and controls in three tasks evaluating different aspects of social cognitive processing. The horizontal dashed line represents chance level

Each group was further analyzed individually. Bonferroni-corrected multiple comparisons (cutoff level of significance $p=0.006$) showed that in the control group, the proportion of correct responses was higher in the facial expression recognition task ($M=0.92$, SD = 0.10) than in the face-cartoon-matching task [$M=0.74$, SD = 0.13; $t(21)=6.2$, $p=0.001$, $d=1.31$; actual power 98.1%] and the face-prosody-matching task [$M=0.81$, SD = 0.13; $t(21)=3.5$, $p=0.006$, $d=0.75$; actual power 78.5%]. However, no difference was observed between the last two tasks [$t(21)=2.2$, $p=0.13$, $d=0.46$]. A similar pattern was observed in the patient group. The proportion of correct responses was higher in the facial expression recognition task ($M=0.75$, SD = 0.13) than in the face-cartoon-matching task [$M=0.53$, SD = 0.17; $t(15)=6.7$, $p=0.001$, $d=1.7$; actual power 98.5%] and the face-prosody-matching task [$M=0.45$, SD = 0.19; $t(15)=7.4$, $p=0.001$, $d=1.9$; actual power 99.2%]. No difference was observed between the last two tasks [$t(15)=1.5$, $p=0.44$, $d=0.38$]. As seen in Fig. 3, the sharper decline in performance between the facial expression recognition task and the other two tasks in the patient group than in the controls drives the group × task interaction. Patients did not perform well in identifying the emotions in isolation (facial expression recognition task), but they performed even worse in context (face-cartoon and face-prosody tasks).

Of most interest was that, despite each patient's performance being weaker than the performance of controls, it was always higher than chance level (since in each task, six responses were possible, the chance-level proportion was 0.166; Fig. 3). This was found to be the case in the facial expression recognition task [$t(15)=17.9$, $p=0.001$, $d=4.5$; actual power 99.9%], the face-cartoon-matching task [$t(15)=8.5$, $p=0.001$, $d=2.1$; actual power 99.6%] and the face-prosody-matching task [$t(15)=6.1$, $p=0.001$, $d=1.5$; actual power 97.0%]. These results suggest that, despite their difficulties in social cognition, the patients did not respond randomly.

## Correlations between cognitive performance, behaviour and the tasks of social cognition

Correlations were conducted separately for each of the two groups. At this aim, the IQ level, the selective attention score from the Sky search task, and the proportion of errors in the overlapping lines task, the arrows task and the orientation task were used for assessing the relationship with cognition. The scores in the five subscales of the ABC-C, the scores of the MDI-C and the aggression scale were used for assessing relations with behaviour. Finally,

since the mixed ANOVA did not reveal any specific effect or interaction involving the six emotions, only the mean proportion of correct responses was considered for each of the three tasks of social cognition. After Bonferroni correction (cutoff level of significance $p = 0.0014$), the only significant finding was a negative correlation between the Arrows task of visual spatial perception and the mean proportion correct responses in the face-prosody task ($\rho = -0.71$) for the control group. This correlation was not significant in the patient group ($\rho = -0.43$). However, the comparison between the correlations did not reveal significant ($z = 0.72$, $p = 0.24$ two-tailed), suggesting that the observed difference between the groups is only artifactual.

### Error patterns in the facial expression recognition task

The proportions of errors for each expected response/given response combination for each group and the results of the comparison between the two groups are presented in Table 2. Patients misrecognized three facial expressions more frequently than controls: sadness was misrecognized as fear ($p = 0.01$), surprise as happiness ($p = 0.05$), and disgust as surprise ($p = 0.045$).

### Error patterns in the face-cartoon-matching task

Patients miscomprehended the nature of several situations depicted in the presented scenes more frequently than controls. First, situations involving sadness, surprise and fear were all misinterpreted as involving anger ($ps = 0.014$, 0.049 and 0.011, respectively). Second, situations involving disgust were misinterpreted as involving sadness ($p = 0.014$) and fear ($p = 0.047$).

### Error patterns in the face-prosody-matching task

Even though, as shown earlier, the face-prosody-matching task was not more difficult than the previous one for either group, the patients mismatched several emotions more frequently than controls. Happiness, sadness, surprise and fear were misinterpreted as being anger (all $ps < 0.021$). Anger, surprise and disgust were misinterpreted as happiness (all $ps < 0.04$). Anger and sadness were misinterpreted as disgust (both $ps < 0.05$). Finally, anger was also misinterpreted as sadness ($p = 0.015$). Anger was, therefore, the emotion that was most miscomprehended, followed by sadness and surprise. However, anger was also the most frequently given response, just as in the face-cartoon-matching task, followed by happiness.

### Correlations between cognitive performance, behaviour and error patterns

As explained earlier, due to the high number of expected response/given response possibilities in the analysis of errors, the number of cells that could have contained values of 0 was important. That was the reason why correlation analyses were impossible to carry out on each individual error pattern. To carry out analyses and to avoid Type I errors, data were collapsed across the three tasks and only the error patterns in which significant differences between the two groups were considered. These errors were clustered as a function of the response given by participants (e.g. whether the real stimulus was surprise, anger or disgust, it was considered as "happiness response" if a participant responded that he/she perceived happiness). Indeed, it can be assumed that the misattribution errors represent the way participants perceived the stimulus and reveal perceptual biases towards one emotion or another). Correlations were conducted separately for each of the two groups. As before, the IQ level, the selective attention score from the Sky search task, and the proportion of errors in the Overlapping lines task, the Arrows task and the Orientation task were used for assessing the relationship with cognition. The scores in the five subscales of the ABC-C, the scores of the MDI-C and the Aggression scale were used for assessing relations with behaviour. After Bonferroni correction (cutoff level of significance $p = 0.0007$), the only significant finding was a negative correlation between the frequency with which a "happiness" response was wrongly given and the Aggression scale ($\rho = -0.78$) for the patient group. This correlation was not significant in the control group ($\rho = -0.12$). The comparison between the correlations revealed significant ($z = 2.28$, $p = 0.01$ two-tailed). This result suggests that the more frequently children/adolescents with 22q11.2DS perceive happiness where there is not (whether on the face, in social contexts or in the voice), the less they exhibit aggressive behaviour. Seemingly, such a regulatory mechanism differentiates 22q11.2DS patients from controls.

## Discussion

The aim of this study was to assess these components of emotional and social cognitive processes in children with 22q11.2DS compared to healthy children and to unravel the way they process social cognitive information, as well as to unravel differences among components of social cognition. A secondary aim was to assess the relationship between some neurocognitive processes, social cognition and behaviour.

**Table 2** Mean (SD) proportion of given responses for each expected response in each of the three tasks used in the present study

| Expected | Given | Facial expression recognition | | | Face-cartoon matching | | | Face-prosody matching | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Response | Response | Controls | 22q11.2DS | *p* value | Controls | 22q11.2DS | *p* value | Controls | 22q11.2DS | *p* value |
| Happiness | *Happiness* | *1.00 (0.00)* | *0.887 (0.262)* | *0.026* | *0.881 (0.159)* | *0.800 (0.263)* | *0.268* | *0.927 (0.131)* | *0.637 (0.344)* | *0.0006* |
| | Anger | 0.00 (0.00) | 0.040 (0.087) | 0.064 | 0.027 (0.093) | 0.012 (0.049) | 0.753 | 0.00 (0.00) | 0.087 (0.125) | 0.003* |
| | Sadness | 0.00 (0.00) | 0.037 (0.108) | 0.171 | 0.036 (0.078) | 0.037 (0.108) | 1.00 | 0.00 (0.00) | 0.037 (0.080) | 0.069 |
| | Surprise | 0.00 (0.00) | 0.025 (0.068) | 0.172 | 0.018 (0.058) | 0.050 (0.115) | 0.486 | 0.036 (0.078) | 0.075 (0.143) | 0.380 |
| | Fear | 0.00 (0.00) | 0.025 (0.068) | 0.163 | 0.018 (0.058) | 0.075 (0.177) | 0.164 | 0.00 (0.00) | 0.062 (0.140) | 0.066 |
| | Disgust | 0.00 (0.00) | 0.00 (0.00) | 1.00 | 0.009 (0.042) | 0.025 (0.068) | 0.556 | 0.027 (0.093) | 0.037 (0.108) | 1.00 |
| Anger | Happiness | 0.00 (0.00) | 0.012 (0.049) | 0.420 | 0.063 (0.155) | 0.162 (0.182) | 0.074 | 0.018 (0.058) | 0.099 (0.126) | 0.019* |
| | *Anger* | *1.00 (0.00)* | *0.940 (0.194)* | *0.197* | *0.781 (0.238)* | *0.624 (0.251)* | *0.06* | *0.827 (0.216)* | *0.525 (0.325)* | *0.002* |
| | Sadness | 0.00 (0.00) | 0.00 (0.00) | 1.00 | 0.054 (0.110) | 0.062 (0.140) | 0.921 | 0.009 (0.042) | 0.087 (0.125) | 0.015* |
| | Surprise | 0.00 (0.00) | 0.012 (0.049) | 0.427 | 0.081 (0.118) | 0.075 (0.143) | 0.962 | 0.090 (0.192) | 0.087 (0.102) | 0.86 |
| | Fear | 0.00 (0.00) | 0.025 (0.068) | 0.171 | 0.009 (0.042) | 0.050 (0.115) | 0.239 | 0.027 (0.070) | 0.062 (0.120) | 0.311 |
| | Disgust | 0.00 (0.00) | 0.025 (0.099) | 0.43 | 0.009 (0.042) | 0.025 (0.068) | 0.575 | 0.009 (0.042) | 0.100 (0.219) | 0.050* |
| Sadness | Happiness | 0.00 (0.00) | 0.037 (0.15) | 0.425 | 0.100 (0.134) | 0.062 (0.095) | 0.340 | 0.009 (0.042) | 0.012 (0.050) | 1.00 |
| | Anger | 0.009 (0.042) | 0.012 (0.049) | 1.00 | 0.072 (0.131) | 0.224 (0.229) | 0.014* | 0.00 (0.00) | 0.087 (0.102) | 0.0008* |
| | *Sadness* | *0.827 (0.271)* | *0.518 (0.316)* | *0.002* | *0.609 (0.168)* | *0.399 (0.301)* | *0.01* | *0.854 (0.153)* | *0.512 (0.386)* | *0.001* |
| | Surprise | 0.00 (0.00) | 0.028 (0.077) | 0.166 | 0.100 (0.134) | 0.125 (0.191) | 0.651 | 0.027 (0.093) | 0.075 (0.143) | 0.276 |
| | Fear | 0.163 (0.266) | 0.406 (0.264) | 0.010* | 0.072 (0.116) | 0.099 (0.178) | 1.00 | 0.109 (0.147) | 0.200 (0.263) | 0.205 |
| | Disgust | 0.00 (0.00) | 0.00 (0.00) | 1.00 | 0.036 (0.100) | 0.087 (0.145) | 0.213 | 0.00 (0.00) | 0.062 (0.095) | 0.008* |
| Surprise | Happiness | 0.00 (0.00) | 0.112 (0.282) | 0.050* | 0.200 (0.185) | 0.312 (0.252) | 0.134 | 0.081 (0.236) | 0.275 (0.341) | 0.04* |
| | Anger | 0.00 (0.00) | 0.00 (0.00) | 1.00 | 0.054 (0.110) | 0.150 (0.154) | 0.049* | 0.018 (0.058) | 0.100 (0.146) | 0.021* |
| | Sadness | 0.009 (0.042) | 0.025 (0.068) | 0.567 | 0.027 (0.070) | 0.075 (0.161) | 0.196 | 0.018 (0.058) | 0.087 (0.206) | 0.164 |
| | *Surprise* | *0.954 (0.173)* | *0.690 (0.345)* | *0.003* | *0.618 (0.268)* | *0.250 (0.247)* | *0.00001* | *0.827 (0.264)* | *0.337 (0.307)* | *0.00001* |
| | Fear | 0.036 (0.132) | 0.087 (0.145) | 0.365 | 0.072 (0.098) | 0.137 (0.189) | 0.254 | 0.054 (0.091) | 0.137 (0.202) | 0.120 |
| | Disgust | 0.00 (0.00) | 0.100 (0.282) | 0.162 | 0.018 (0.058) | 0.075 (0.100) | 0.056 | 0.00 (0.00) | 0.050 (0.115) | 0.072 |
| Fear | Happiness | 0.00 (0.00) | 0.012 (0.049) | 0.427 | 0.072 (0.131) | 0.125 (0.143) | 0.347 | 0.018 (0.058) | 0.05 (0.089) | 0.371 |
| | Anger | 0.018 (0.058) | 0.037 (0.080) | 0.623 | 0.027 (0.093) | 0.150 (0.171) | 0.011* | 0.009 (0.042) | 0.075 (0.100) | 0.014* |
| | Sadness | 0.181 (0.238) | 0.315 (0.191) | 0.061 | 0.136 (0.178) | 0.150 (0.212) | 0.853 | 0.200 (0.254) | 0.275 (0.240) | 1.000 |
| | Surprise | 0.036 (0.100) | 0.037 (0.15) | 1.00 | 0.090 (0.119) | 0.075 (0.143) | 0.777 | 0.127 (0.180) | 0.087 (0.206) | 0.526 |
| | *Fear* | *0.772 (0.264)* | *0.600 (0.273)* | *0.059* | *0.700 (0.300)* | *0.450 (0.368)* | *0.03* | *0.663 (0.334)* | *0.412 (0.236)* | *0.014* |
| | Disgust | 0.009 (0.042) | 0.012 (0.05) | 1.00 | 0.018 (0.058) | 0.05 (0.089) | 0.374 | 0.00 (0.00) | 0.037 (0.080) | 0.063 |
| Disgust | Happiness | 0.00 (0.00) | 0.00 (0.00) | 1.00 | 0.018 (0.058) | 0.012 (0.049) | 1.00 | 0.018 (0.058) | 0.112 (0.162) | 0.007* |
| | Anger | 0.00 (0.00) | 0.025 (0.099) | 0.420 | 0.063 (0.155) | 0.137 (0.202) | 0.261 | 0.054 (0.140) | 0.099 (0.126) | 0.339 |
| | Sadness | 0.00 (0.00) | 0.00 (0.00) | 1.00 | 0.009 (0.042) | 0.075 (0.100) | 0.014* | 0.090 (0.160) | 0.137 (0.227) | 0.428 |
| | Surprise | 0.00 (0.00) | 0.075 (0.177) | 0.045* | 0.018 (0.058) | 0.062 (0.120) | 0.159 | 0.063 (0.143) | 0.075 (0.100) | 0.803 |

**Table 2** (continued)

| Expected | Given | Facial expression recognition | | | Face-cartoon matching | | | Face-prosody matching | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Response | Response | Controls | 22q11.2DS | *p* value | Controls | 22q11.2DS | *p* value | Controls | 22q11.2DS | *p* value |
| | Fear | 0.009 (0.042) | 0.012 (0.049) | 1.00 | 0.027 (0.070) | 0.099 (0.126) | 0.047* | 0.045 (0.105) | 0.099 (0.126) | 0.181 |
| | *Disgust* | *0.990 (0.042)* | *0.903 (0.235)* | *0.092* | *0.863 (0.264)* | *0.612 (0.296)* | *0.01* | *0.727 (0.335)* | *0.425 (0.308)* | *0.010* |

*p* values (bicaudal) were obtained through permutation tests with 5000 permutations per task. Asterisks denote significant differences ($p \leq 0.05$) between controls and 22q11.2DS patients. Text in italics represent matched expected-given (i.e. correct) responses without group differences to be represented since specific analyses were carried out

## Overall performance

In the present study, patients with 22q11.2DS presented with significant impairments in the processing of emotional and social information compared to healthy controls in recognizing facial expressions, interpreting visually depicted social interactions and emotional prosody through dialogues. Impairment in the recognition of emotional facial expression has already been demonstrated in the literature [2], but our study is the first in which deficits in attributing emotions, both to characters involved in visually presented social interactions and to characters in aurally presented dialogues, are highlighted. This suggests that social cognitive processing in 22q11.2DS is far more complex than just perceiving and recognizing isolated features on faces. Our patients performed even worse in the cartoon and prosody tasks than in the face recognition task. These two tasks are more complex, since they require selecting multiple relevant cues and integrating them with acquired knowledge [18] to form a globally coherent image of what occurs and what the characters' emotional experiences are in each trial. It may be suggested that in attempting to perceive and interpret the nature of social interactions, through either visual or auditory cues, patients with 22q11.2DS have great difficulty and frequently misinterpret what happens. Another, complementary interpretation is that the drop in performance in the two more complex tasks could result from limitations in the processing of multiple target characters. Indeed, both the face-cartoon and the face-prosody-matching tasks involve several characters and also several pieces of secondary information to take into account. The multiplicity of target characters and information could probably exceed the processing capacity of patients and result in decreased performance. Of most interest was that all the above-mentioned observations were made even after having statistically controlled for the impact of age, gender and IQ level, suggesting that these patients face genuine social cognitive impairments that are independent from global cognitive efficiency. Furthermore, correlational analyses failed to find any relationship between performance in the three tasks of social cognition and more basic visual perceptual and attentional processes, suggesting that the involvement of such mechanisms in social information processing in 22q11.2DS may be limited.

## Facial expression recognition

The analysis of the proportion of correct responses did not reveal any differential impairment in recognizing facial expressions as a function of the emotion assessed, as suggested through the extant literature [7, 8, 10, 11, 41]; rather, we found a more general impairment in 22q11.2DS compared to controls. However, the analysis of error patterns showed that 22q11.2DS patients misinterpreted three facial

expressions more frequently than controls: sadness was mistaken as fear, surprise as happiness, and disgust as surprise. These confusions seem to relate to the visual details of the faces, such as the mouth width and the angle of the eyes and eyebrows (when sadness was confused with fear), the configuration of the mouth (between surprise and happiness), and the configuration of the eyes and the eyebrows (when disgust was misrecognized as surprise). However, this is only a hypothesis, and the present study does not offer any data to support it directly. Even though we did not use eye-tracking techniques in the present study, our findings do not support the assumption of an overall impaired pattern of face exploration, as has been proposed by some authors [8, 9, 12, 13], since this would result in a rather widespread and non-regular pattern of errors. Actually, the confusion is probably due to subtle visual details and could relate to perceptual or attentional impairments other than in visual scanning [13]. Yet, our study failed to find any relationship between perceptual or attentional impairments and recognition of emotions. Thus, it is not yet clear whether and how and to what degree specific cognitive impairments, such as those in visual perception and processing, influence facial expression recognition in 22q11.2DS.

## Face-cartoon matching

The face-cartoon-matching task requires understanding and interpretation of visual scenes involving one of the six target emotions. This test encompassed more complex social cognitive processes than the facial expression recognition task, and thus involves the emotional dimension of ToM, also called the affective theory of mind [15]. This ability seems to be disordered in children and adolescents with 22q11.2DS [1, 6, 23, 42, 43], and our results confirm this. A recent study [1] suggested that such difficulties might be attributed to other abilities, like inferring the sequence of events when responding. Our results cannot be attributed to such processes since the face-cartoon-matching task was designed to decrease the involvement of such sequencing abilities as much as possible. Furthermore, the fact that the difference between the two groups was still there after controlling for IQ level suggests that there is a genuine deficit in the specific social cognitive processes involved.

The analysis of error patterns revealed that compared to controls, 22q11.2DS patients more frequently misinterpreted emotional situations involving sadness, surprise and fear as involving anger, and again compared to controls, situations involving disgust were more frequently misinterpreted as involving sadness or fear. The first category of confusion indicates that children with 22q11.2DS tend to use a simple attractive/repulsive—or happy/angry—dichotomy to interpret social situations. In typically developing children, emotion recognition improves with age. In a study focused on children from 4 to 11 years old, Chronaki et al. [44] showed that sadness recognition was delayed across development relative to anger and happiness. Our results may indicate that patients with 22q11.2DS have a delay in the ability to accurately differentiate specific emotions in the case of understanding complex social scenes [6, 45]. The use of the face-cartoon-matching task in a longitudinal study or an age transversal study would provide important insights into the developmental delays in 22q11.2DS.

The second category of confusion showed that compared to the controls, 22q11.2DS patients more frequently misinterpreted than controls the situations of disgust as involving sadness or fear. According to Reeve [46], negative emotions constitute a global response to threats. More specifically, while disgust constitutes a rejection response to a threat, fear marks a defensive response to the threat, and sadness, which is expressed after the threat, may be considered to result from it. In 22q11.2DS, the confusion of these emotions could be related to difficulties in differentiating specific responses to threats. This is an entirely new finding and should be further investigated to understand what may underlie such a difficulty in differentiating responses to threats.

## Face-prosody matching

The face-prosody-matching task assessed the ability to understand the emotion expressed by two characters in their dialogue while ignoring the propositional content of those dialogues. It thus tested prosodic emotion recognition. The results showed that children with 22q11.2DS present with a reliable impairment in matching facial expressions to the vocal emotions expressed through dialogue. In the literature, only one paper reported data concerning the vocal components of emotional processing in a population of 22q11.2DS patients [14]. The results showed no difference between the 22q11.2DS patients and controls in recognizing happiness, sadness, anger and fear through the tone of the voice. In the study by Shashi et al. [14], accuracy for specific emotions was not analyzed, and this may be one reason why such impairment was not found. Furthermore, the authors interpreted the lack of difference between 22q11.2DS patients and healthy children as resulting from a split in the IQ indices in a part of their population of patients, with high rates of non-verbal learning deficits, which would provide a relative strength in verbal abilities and thus a better auditory discrimination of all stimuli, including emotions. The authors also proposed that they might be underpowered to detect differences between the 22q11.2DS and control groups. In the present study, we checked that the participants with 22q11.2DS had both normal ENT assessments and an IQ within the normal range, as assessed by a non-verbal measure [24], but we did not precisely test verbal and non-verbal

learning abilities. Furthermore, the results were controlled for IQ level. We are, therefore, confident that the deficits observed here can be attributed to difficulties with social cognitive information processing rather than to IQ or ENT disturbances. Although verbal abilities were not involved in the task we used here (since vocal emotions were completely independent from the verbal content of the dialogues), future studies could use a measure of verbal learning to unravel its relationship with emotional voice recognition.

In addition to an overall decreased accuracy compared to the controls, 22q11.2DS patients also displayed some consistent error patterns, suggesting that despite the amount of confusion, it is not due to random responses. The analysis of the confusion allowed further examination of this impairment. Compared to the results for the controls, four vocal emotions were more frequently misinterpreted as anger; these were happiness, sadness, surprise and fear. Three others were misinterpreted as happiness: anger, surprise and disgust. Anger and sadness were misinterpreted as disgust. Finally, anger was also misinterpreted as sadness. Once again, such an error pattern is not compatible with a general impairment nor a limitation in processing multiple target characters during the task.

Interestingly, the two most frequent responses that gave rise to such confusion involved anger and happiness, and this brings to mind the attractive/repulsive—happy/angry—dichotomy that has been suggested to account for performance in the face-cartoon-matching task. However, it is also of interest that the two least frequent responses (i.e., disgust and sadness) bring to mind the second confusion category found in the face-cartoon-matching task, which entailed difficulties in differentiating specific responses to threats [46].

The observed error patterns suggest that difficulties in understanding and logically reasoning about social situations in 22q11.2DS might be related to two types of disturbances: a tendency to coarsely classify social situations into two opposing categories (attractive/repulsive) and a more specific difficulty in differentiating emotions that are associated with threats. Whether these two types of disturbances are hierarchized or not is difficult to know, even though in both the face-cartoon- and face-prosody-matching task responses, those entering the first type were more frequent than those entering the second one. The first type of disturbance surprisingly brings to mind the distinction between the systems of behavioural activation and inhibition in Gray's [47] reinforcement sensitivity theory. The former is sensitive to reward and produces responses of approach, whilst the latter is triggered by fear and signals of punishment and produces avoidance. It is similar to the notion that patients with 22q11.2DS think mostly on the basis of cues of reward (i.e., attractive) and punishment (i.e., repulsive) in a coarsely dichotomous fashion. The two systems may affect the shaping and encoding of developmental experiences, such as socialization and understanding of social interactions, and lead to abnormal comprehension of those interactions. The behavioural activation and inhibition systems hypothesis seems to be the most adequate interpretation of the results and further investigation is necessary for confirming or refining our observations. This also might explain why error patterns in the facial expression recognition task were different, since that specific task does not involve logical social reasoning and interpretation of complex situations.

## Social cognition and behaviour

The present study globally failed to evidence correlations between performance and error patterns in the tasks of social cognition, tasks assessing more basic cognitive processes, and parent-completed scales of everyday behaviour. The literature does not provide any convincing evidence that deficits in social cognition tasks are associated with problematic behaviour in 22q11.2DS. Indeed, social cognitive impairments have been studied in relationship with the emergence of psychotic symptoms in adults [3] and, to our knowledge, only a single study reported an association between social cognition and behaviour in 22q11.2DS [6]. The absence of reliable results in the present study may be due to the severe restrictions imposed by the procedures of statistical correction. However, an isolated finding was that the more frequently 22q11.2DS patients reported misperceiving other emotions as being happiness, the less the degree of aggressive behaviour described by their parents. Such thing was not found in controls. This may constitute a real difference in the socio-emotional functioning of 22q11.2DS patients since the degree of aggression was not found to be different between the groups. A study by Penton-Voak et al. [48] demonstrated that experimentally biasing the perception and recognition of emotions towards happiness led to changes in self-reported and independently-rated aggressive behaviour in adolescents with high-risk of criminal and antisocial behaviour. This is compatible with the above-mentioned result. Our finding may reflect the presence of a spontaneously developed positivity-oriented emotional mechanism that would help regulate some kinds of social interactions in 22q11.2DS. Are we facing the consequence of a behavioural activation system [47] that developed differently as to shape socialization and understanding of social interactions? However, this isolated finding may also reflect a false positive, and caution is needed when interpreting it, especially since the association between social cognition and behaviour is not always found in the extant literature.

## Limitations

One possible limitation of our study is that it did not use natural stimuli such as photographs or audio recordings of real-life

dialogues. The fact that all stimuli were especially designed for this study is instead a strength because it enables the comparison of the three tasks. In addition, it enables controlling for noise introduced by natural stimuli, such as contrast, saliency, complexity, as well as confounds related to facial characteristics that are irrelevant to the emotional facial expression, such as gender, ethnicity, age, attractiveness, moles, wrinkles and freckles. Furthermore, natural stimuli for the face-cartoon- and the face-prosody-matching tasks are impossible to obtain. Finally, all facial expressions used in the present study were exaggerated to better emphasize their main traits, to render them more evocative, and to focus children's attention on the traits that were relevant for the tasks [33].

Several studies have suggested that impaired facial expression recognition in 22q11.2DS might be due to disordered visual scanpaths [8, 9, 12] or to deficits in perceptual processes [13]. These two accounts are difficult to disentangle, since the former may condition the efficiency of the latter, and vice versa. Although our findings did not support the assumption of a consistently impaired pattern of face exploration, it is difficult to be sure that this was not the case, given that no eye-tracking techniques were used. In addition, whether perceptual processes have an impact that goes beyond face identification is still a subject of investigation, and further studies are required to understand the degree to which such processes contribute to social cognitive impairments. One possible methodological limitation is that, during the training trial of the facial expression recognition task, the experimenter corrected the child's response if incorrect. This adds a learning aspect to the task that may make it difficult to interpret the results in terms of facial expression recognition. However, this procedure was the best for allowing participants to know the emotion label that goes with each facial expression. Indeed, during the pilot study, it was found that some expressions were known, correctly recognized and associated with specific situations but that their names were not known by all participants.

Finally, we did not assess the contribution of higher executive functions to social cognition impairments. Although this was not within the scope of this study, the fact that the observed patterns of performance were independent from the g-factor (as assessed by Raven's Coloured Progressive Matrix IQ test) suggests that at least some of these impairments are not dependent on other processes. This aspect should be further investigated using specific protocols, as should the relationship between impairments in emotional processing and symptomatology.

## Conclusions

To conclude, this study showed that, compared to control participants, children with 22q11.2DS have significant social cognitive deficits that are independent of age, gender and IQ level. First, our results suggested that 22q11.2DS individuals have impaired emotional facial expression processing compared to their typically developing peers. Even though this impairment could be related both to poor visual exploration patterns, as highlighted by eye-tracking studies [8–11], and to cognitive skills, such as visual perception and processing [13], our study failed to find such a relationship. Second, 22q11.2DS patients presented with significant difficulties in a task requiring more complex social cognitive processes, such as affective ToM ability, assessed through the face-cartoon- and the face-prosody-matching tasks. Finally, this is the first time a deficit in interpreting vocal emotions has been shown in 22q11.2DS. However, some studies have suggested that cognitive deficits, notably, impaired visual perception and executive control, might best explain the impairments in complex social cognitive processes rather than specific difficulties with social stimuli in 22q11.2DS [1, 6]. Assessing the role of these functions in social cognitive difficulties was not within the scope of the present study. Instead, the aim was to unravel the way 22q11.2DS patients understand such complex situations and the way they respond. The analysis of error patterns in the face-cartoon- and face-prosody-matching tasks suggested that difficulties in 22q11.2DS might be related not only to a tendency to coarsely categorize social situations as either attractive or repulsive but also to difficulties in differentiating emotions that are associated with threats. The important insights into social cognitive processes, such as the kind of analyses being performed, allow us to estimate the specific techniques of remediation of social abilities that can be targeted and developed. For instance, the fact that 22q11.2DS patients misperceive some emotions as being happiness is related to decreased aggressive behaviour. Experimental studies in other populations suggest that similar effects may be obtained through training and adaptation procedures. This gives hope that remediation procedures be developed and even generalize beyond the specific link between perceiving happiness and toning down aggressive behaviour. Future research should not only further explore the relationship between basic cognitive processes and higher order cognition but also focus on the way 22q11.2DS patients process emotional information to understand social contexts, as well as the way these deficits contribute to psychopathology and functioning in daily life. Finally, the fact that the protocol is quite easy for children to complete, despite the possibility that their language abilities might be weak, opens new perspectives on the assessment of social cognition in other pathological conditions.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical approval** The study was conducted in accordance with the Declaration of Helsinki and was approved by the local Ethics Committee (CPP Lyon-Sud Est IV, No. 15/041; ANSM, No. 2017-A00881-52; NCT03284060).

**Informed consent** Informed written consent was obtained from all children and from their parents (or legal guardians).

**Data repository** The data can be found at https://recherche.univ-lyon2.fr/etmeco/data/Peyroux-22q11-Data.zip.

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## L’impact des symptômes psychotiques sur la perception émotionnelle

L’étude 4 a montré que les enfants ayant un 22q11.2DS avaient de plus faibles performances que des enfants neurotypiques dans la reconnaissance des émotions faciales sur visages seuls, en contexte ou via la prosodie. Rappelons que les adolescents ayant un 22q11.2DS ont un risque élevé de développer des symptômes psychotiques (Monks et al., 2014). La littérature sur les liens existants entre troubles de la cognition sociale et symptomatologie psychotique sont hétérogènes. En effet, certains auteurs attestent de l’impact de symptômes psychotiques sur les compétences en cognition sociale (Jalbrzikowski et al., 2012; Weinberger et al., 2016, 2018) tandis que d’autres ont retrouvé chez les adultes porteurs d’un 22q11.2DS des difficultés mais indépendamment de la présence de symptômes psychotiques (Accinni et al., 2022; Buzzanca et al., 2023).

Ainsi, l’objectif de l’étude 5, a été de faire la lumière sur les liens potentiels entre symptômes psychotiques précoces et compétences dans le champ de la perception émotionnelle chez des enfants porteurs d’un 22q11.2DS et ayant moins de 13 ans. Pour cela, des enfants porteurs d’un 22q11.2DS ont été recrutés et assignés à deux groupes distincts : (1) présentant des symptômes psychotiques, (2) ne présentant pas de symptômes psychotiques. Des enfants neurotypiques ont également été inclus dans l’étude. Chaque enfant s’est vu présenté le même protocole expérimental que celui de l’étude 4.

# Does the presence of early psychotic symptoms impact emotion perception in different modalities in 22q11.2DS?

Marie-Noëlle BABINET, Eloïse MASOERO, Laurette TRINCKQUEL, Caroline DEMILY, & George A. MICHAEL

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**Abstract**

Impairments in social cognition have been frequently reported in 22q11.2 deletion syndrome (22q11.2DS) and are thought to be a hallmark of difficulties in social interactions. The risk of 22q11.2DS for developing early psychotic symptoms or even schizophrenia in adulthood is significant. Studies that have studied the links between difficulties in social cognition and the risk of psychosis show contradictory results. The present study aims to investigate emotion perception processes in 22q11.2DS as a function of the presence of psychotic symptoms in children under the age of 13. Thirty-eight children with 22q11.2DS and fifty-four healthy controls completed one task of facial expression recognition, one task of attribution of facial expressions to faceless characters involved in visually presented social interactions, and one task of attribution of facial expressions to characters involved in aurally presented dialogues. Children with 22q11.2 were assigned to one of two groups: psychotic children and non-psychotic children. Patients performed worse than controls in all three tasks of emotion processing, and even worse in the second and third tasks, but regardless psychotic symptomatology. Emotion perception, taken individually, may therefore not be a useful marker for the development of psychosis. In view of the data regarding error patterns in facial emotion perception and the possible link to impaired visual face scanning, future studies in children at high risk of psychosis (e.g., 22q11.2DS) should use eye-tracking to better understand the origin of the difficulties.

**Keywords**: 22q11.2 deletion syndrome; emotional processes; early psychotic symptoms

## 1. Introduction

22q11.2 Deletion Syndrome (22q11DS) represents the most common multisystemic syndrome with a chromosomal Copy Number Variation as its etiologic factor. Its incidence ranges from 1:3000 to 1:6000 new births according to literature (Botto et al., 2003; Grati et al., 2015). A significant proportion of behavioural disorders during development (McDonald-McGinn et al., 2015) and an increased incidence of mental disorders (Pontillo et al., 2019) have been observed in people with 22q11.2DS compared to the general population. The risk of 22q11.2DS for developing a psychotic illness during the lifespan, including schizophrenia and schizoaffective disorder, varies across various studies from 23% to 43% (Bassett et al., 2003; Murphy, 2002; Schneider et al., 2019). 22q11DS is considered as a valuable, simplified biological model for studying early neuropsychiatric disorders (Fiksinski et al., 2017; Lattanzi et al., 2018).

The neurocognitive profile of 22q11.2DS varies both across individuals and within the same individual during their lifespan (Vorstman et al., 2015). A borderline cognitive level (IQ from 70 to 84) and a moderate intellectual disability have been reported in one-third of people with 22q11.2DS (Chow et al., 2006). Furthermore, it is now well documented that children and adults with 22q11.2DS have poorer social competences, including mood lability, shyness, and difficulties in initiating and maintaining social relationships, compared with typically developing young people (Campbell et al., 2015). These social dysfunctions could be partly underlain by impairments in social cognitive processes (Lattanzi et al., 2018; Peyroux et al., 2020; for a review, see Norkett et al., 2017), and could also be linked to the emergence of psychosis (Jalbrzikowski et al., 2012). In fact, significant evidence about social cognition deficits compared to other idiopathic neuropsychiatric conditions, even once corrected for intellectual abilities, has been reported (Jalal et al., 2021, Peyroux et al., 2020). However, some authors (Glaser et al., 2010) explain these deficits by the level of IQ.

Social cognition consists of a large set of cognitive functions aimed at social inference and other's mental state representation (Gottesman & Gould, 2003; Green et al., 2019). Processing and understanding social information also require collecting and processing cues beyond facial expressions, such as postural and vocal information that is present in social interactions or prosody. In most cases, the neuropsychological tasks that have been used to study emotion recognition in 22q11.2DS have been based on emotional labelling of people depicted in photos (Campbell et al., 2010) or in representations of a cognitive mental states described in vignettes

(Jalbrzikowski et al., 2012). Little has been done to investigate the attribution of an emotion in context or the understanding of more common social contexts, and when it has been done, it proved difficult to disentangle the social cognitive difficulties from executive deficits (Campbell et al., 2015). Concerning emotional prosody, only two studies have compared the performance of patients with 22q11.2DS to that of healthy controls (Peyroux et al., 2020; Shashi et al., 2012), and the results are contradictory. Some authors found similar performance between 22q11.2DS and controls (Shashi et al., 2012) while others found a reliably lower performance in children with 22q11.2DS (Peyroux et al., 2020).

What about understanding the links between difficulties in social cognition and the risk of psychosis? The majority of studies conducted in adolescents or young adults did not find any correlation between social cognition and risk of psychosis, even after controlling for IQ (Tang et al., 2017; Yi et al., 2015). The existing studies regularly contradict each other. For instance, Jalbrzikowski (2012) investigated social and neurocognitive abilities as related to positive and negative symptoms of psychosis. Emotion recognition emerged as an indicator of negative symptoms of psychosis. Other authors explained that 22q11.2DS individuals with a psychotic disorder had more severe deficits in facial emotion recognition than 22q11.2DS without psychotic disorder (Weinberger et al., 2016, 2018). In recent studies conducted by Accini et al. (2022) and Buzzanca et al. (2023), when they compared 22q11.2DS adults with and without psychosis, they found differences in social cognition, which was impaired in people with psychotic symptoms. This is a reminiscent of what is observed in patients with schizophrenia regardless of psychotic symptomatology. It thus is appeared that despite the interest of several studies on this topic, the findings in conclusions are inconsistent. Moreover, to date no study has tried to clarify these links between psychosis and social cognition in children under the age of 13.

Therefore, the aim of this study was to investigate emotion perception processes in 22q11.2DS as a function of the presence of psychotic symptoms. A task of facial expression recognition, a task of face-cartoon-matching, and a task of face-prosody-matching were proposed to three groups: (i) the first group consisted of children with 22q11.2DS and psychosis, (ii) the second of children with 22q11.2DS without psychosis, and (iii) the third of a healthy control group without any history of genetic or psychiatric disorder. We expected to observe significant differences in emotion perception between the groups. We hypothesized that, independently of the presence of psychotic symptoms, children with 22q11.2DS would have lower performance

than control children in all three tasks (Peyroux et al., 2020). However, given the inconsistencies found in the literature, it is difficult to hypothesize whether children with psychotic symptoms would have lower performance than those without symptoms (Jalbrzikowski et al., 2012; Weinberger et al., 2016). Furthermore, we hypothesized that the IQ level would explain only a small part of the differences between the groups.

## 2. Method

### 2.1 Participants

Thirty-eight children with 22q11.2DS (mean age in years = 8.47, SD = 2.21) and fifty-four healthy controls (mean age in years = 8.85, SD = 2.47) took part in the study. Children with 22q11.2 were assigned to one of two groups: psychotic children (n = 13) and non-psychotic children (n = 25) on the basis of an interview (see Procedure Section). The three groups (controls, non-psychotic children and psychotic children) were matched in age and gender (Table *1*). All children were recruited through the Center of Rare Diseases Reference, GénoPsy, in Lyon (France). Participants with the following criteria were excluded from the study: (i) difficulties in understanding or lack of command of the French language, (ii) significant comorbid medical conditions, such as the presence or history of neurological disorders affecting the cerebral function, (iii) presence of a severe visual or hearing impairment interfering with the assessment. The diagnosis of 22q11.2DS was confirmed in all patients by fluorescence in situ hybridization (FISH) and complete genomic hybridization (CHG-Array). Finally, an IQ measure (assessed with Raven's Coloured Progressive Matrices) (John & Raven, 2003) was proposed to all participants. This is a non-verbal test of fluid intelligence, all items of which consist of visual geometric designs with a missing part. The participant is given six choices to pick from and fill in the missing part. This tool was chosen because it involves the same visual scanning process and motor pointing processes used in the tasks assessing emotion perception (see Emotion Perception Assessment section). Each parent and children signed an informed consent and the study was conducted in accordance with the Declaration of Helsinki and was approved by a national Ethics Committee (CPP Est-II, No. 2020-A01370-39; NCT04639388).

### 2.2 Procedure

For children with 22q11.2DS, the screening interview Psychosis section of the French version of the K-SADS-PL (Thümmler & Askenazy, 2018) was proposed by a doctor to the family group (parent and child). During this screening, two main themes were addressed by the doctor: (i) auditory and visual hallucinations and (ii) delusions. For each theme, the doctor assessed whether the symptoms were absent (scored 1), subclinical, i.e. suspected or probable symptoms (scored 2), or clinical, i.e. presence of some of the symptoms (scored 3). Subsequently, if a score of 3 were obtained for one of the two previous themes, this means that there was an argument in favour of Schizophrenia Spectrum Disorder (SSD) and the child was assigned to the psychotic group.

### 2.3 Emotion perception assessment

The protocol used was the same as that described in the study of Peyroux and colleagues (2020). Emotion perception processes were assessed with a protocol intended for children and were composed of three tasks: facial expression recognition task, face-cartoon-matching task and face-prosody-matching task. Visual stimuli were produced by a graphic designer using Photoshop CS5 software on a Wacom Bamboo A5 graphic tablet. All stimuli were validated through a sample of adults beforehand. The first reason was to control at best all aspects of stimuli and avoid typical problems that exist with natural stimuli, such as photographs. These problems involve contrast, saliency, visual and auditory complexity. The second reason was to make all three tasks directly comparable since the response mode and the stimuli used for the responses were strictly identical in all three tasks. The third reason was that it was impossible to create natural stimuli for the face-cartoon-matching task and also for the face-prosody-matching task. The last reason was that some studies (Brechet, 2017; MacDonald et al., 1996) showed that young children have more difficulties recognizing facial expressions on photographs than on drawings of faces. The use of drawings minimizes confounds related to facial characteristics that are present in natural photographs but irrelevant to the emotion. These include gender, age, attractiveness, and ethnicity, as well as physical characteristics such as wrinkles and freckles. All participants were tested in a silent room.

#### 2.3.1 Facial expression recognition task

The aim of the first task was to assess the identification of isolated facial expressions. Six hairless and genderless cartoon faces expressing the six basic universal emotions were drawn

with black ink according to the traits listed by Ekman and Friesen (Ekman & Friesen, 1971). The emotions were happiness, surprise, sadness, anger, disgust and fear. The six faces were presented simultaneously on A4 landscape-oriented sheets of white paper in two rows of three faces each (Fig. *1*). Five sheets (i.e. a total of 30 stimuli, with each expression being presented 5 times) were produced, and the spatial location of each facial expression changed from 1 sheet to the next. For each sheet, the participant was required to point to the face that looked happy, sad, disgusted, angry, surprised or fearful. After the final sheet, the examiner proceeded to point to and simultaneously name each one of the faces, even if all responses given by the participant were correct. This aimed to reinforce the identification of each facial expression for subsequent tasks. The task lasted approximately 5 min.

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INSERT FIGURE 1 HERE PLEASE

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### 2.3.2 Face-cartoon-matching task

The aim of this task was to assess the ability to understand the context of visually presented scenes (Kolb et al., 1992) involving one to three faceless characters in situations where emotions were expressed. The scenes were drawn with black ink on white A4 landscape-oriented sheets. The target character was always wearing orange clothing to be immediately and easily detected and identifiable. The target character was a boy in half of the trials and a girl in the other half. Thirty scenarios were included in the test, depicting various everyday situations. Each of the six facial expressions matched the emotion expressed by the target character, and for each expression, five scenarios were presented. A sixth scenario, which was associated with happiness, was used as both an example and a training trial. At the bottom of each scene, the six isolated facial expressions that were previously used were presented in a row that served as the answer choices (Fig. *2*). The participant was required to point to the face the target character would make in each scene presented as quickly and as accurately as possible. The task lasted approximately 20 min.

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INSERT FIGURE 2 HERE PLEASE

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### 2.3.3 Face-prosody-matching task

The aim of this task was to assess the ability to understand the emotional context of aurally presented dialogues involving two characters. The dialogues always consisted of three sentences, the propositional content of which contained no emotion-related words (i.e., "first character: There are spoons on the table. Second character: three chairs are also there. First character again: and the window is open.") (Ross et al., 1997). However, all three sentences were expressed with vocal emotion, and for each dialogue, the expressed vocal emotion was the same for all three sentences (e.g., all three sentences were expressed with anger). The dissociation between the propositional content and the emotional prosody aimed to drastically diminish any interference between the two. Thirty dialogues were created, 5 for each of the 6 basic emotions. A final dialogue (in which happiness was expressed) was created and used as an example and a training trial. The six isolated facial expressions used in the first test were used for the responses. They were presented on an A4 landscape oriented white sheet, were placed on the table in front of the participant and were visible throughout the whole test. The participant was required to point to the face the characters would make in each dialogue. He/she could answer whenever he/she wanted without waiting for the end of the dialogue and he/she was asked to answer as precisely as possible. The task lasted less than 10 min.

## 2.4 Statistical analyses

Statistical analyses on demographic characteristics and IQ measure were performed with an analysis of variance (ANOVA, $\alpha = .05$, throughout) and the Chi square test ($\chi^2$). The proportion of correct responses on the three tasks involving emotion perception processes was analysed through a mixed analysis of variance (ANOVAs, $\alpha = .05$, throughout) with the type of tasks (facial expression recognition, face-cartoon-matching and face-prosody-matching) and emotion (happiness, anger, sadness, surprise, fear, disgust) as within-participants factors, and the group (controls, non-psychotic and psychotic) as between-participants factor. The Greenhouse–Geisser sphericity correction was applied whenever necessary. Partial eta-squared ($\eta^2_p$) coefficients were used to express effect sizes. Multiple post-hoc comparisons were conducted using the Holm test. Statistics were computed using JASP (JASP Team, 2022).

# 3. Results

### 3.3 Participants' characteristics

No difference was found in age ($F(2,90) = 0.29$, $p = .75$, $\eta^2_p = .01$). A difference was, however, found regarding the IQ with patients (psychotic and non-psychotic) scoring lower than controls ($F(2,90) = 56.58$, $p < .001$, $\eta^2_p = .56$). Finally, no group difference was found in terms of the percentages of boys and girls ($\chi^2(2) = 3.08$, $p = .21$), but boys outnumbered girls in psychotic and non-psychotic groups. These demographic characteristics are presented in Table *1*.

### 3.4 Emotion perception

The main effect of group was revealed to be significant [$F(2,89) = 23.62$, $p < .001$, $\eta^2_p = .35$], with the overall proportion of correct responses being lower for the two groups of patients (psychotic children: mean = 0.64, SD = 0.17; non-psychotic children: mean = 0.63, SD = 0.16) than for the controls (mean = 0.82, SD = 0.1). No significant difference was observed between psychotic and non-psychotic children. When the IQ level was used as a covariate in order to unravel its contribution on emotion perception (Badoud et al., 2017; Peyroux et al., 2020), the percentage of variance explained was of 18.8% of the main effect of group.

A significant group*task interaction effect was observed, $F(3,147) = 3.27$, $p = .008$, $\eta^2_p = .07$. The percentage of variance explained by IQ level when used as a covariate was only of 2%. Post-hoc analyses showed that in the control group, the proportion of correct responses was higher in the facial expression recognition task (mean = 0.95, SD = 0.08) than in the face-cartoon-matching task (mean = 0.76, SD = 0.13) and in the face-prosody-matching task (mean = 0.75, SD = 0.19) (all *ps* < .001). However, no difference was observed between the last two tasks. A similar pattern was observed in non-psychotic and psychotic children's group. The proportion of correct responses was higher in the facial expression recognition task (non-psychotic children : mean = 0.81, SD = 0.16; psychotic children: mean = 0.84, SD = 0.15) than in the face cartoon-matching task (non-psychotic children : mean = 0.57, SD = 0.18; psychotic children: mean = 0.6, SD = 0.19) and the face-prosody-matching task (non-psychotic children : mean = 0.49, SD = 0,24; psychotic children: mean = 0.5, SD = 0.21) (all *ps* < .001). No difference was observed between the last two tasks. As seen in Fig. *3*, the sharper decline in performance between the facial expression recognition task and the other two tasks in the patient groups (non-psychotic and psychotic children) than in the controls drives the group*task interaction. Patients, regardless of psychotic symptomatology, did not perform well in

identifying the emotions in isolation (facial expression recognition task), but they performed even worse in context (face-cartoon and face-prosody tasks).

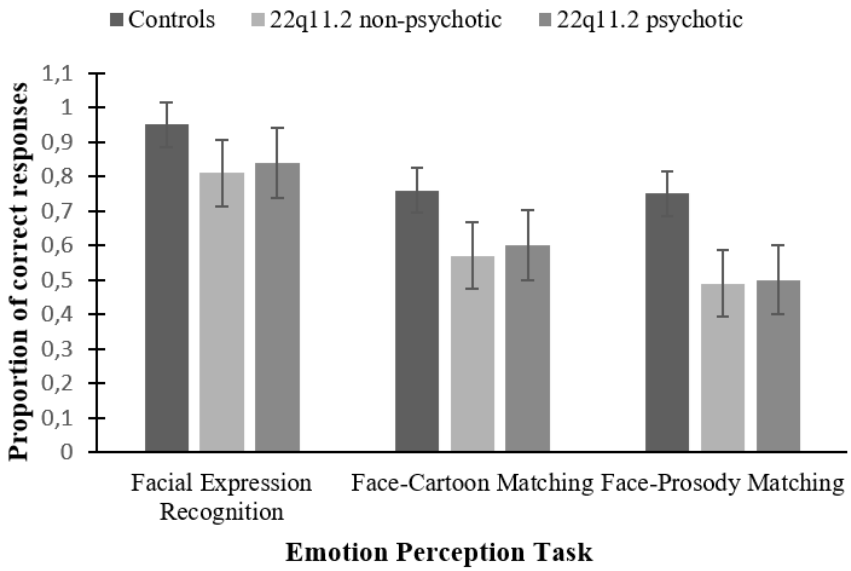


Fig 3. Mean proportion (±1 standard error of the mean) of correct responses given by 22q11.2DS patients non-psychotic and psychotic and controls in three tasks evaluating different aspects of emotion perception processing.

A significant group*task*emotion interaction effect was observed, $F(15,672) = 2.0$, $p < .05$, $\eta^2_p = .043$. The percentage of variance explained by IQ level when used as a covariate was only of 1%.

Partial analyses of variance were conducted on each task. In the facial expression recognition task, a group*emotion interaction was found ($F(6,298) = 4.04$, $p < .001$, $\eta^2_p = .08$), and post-hoc analyses showed no significant difference among the three groups for happiness, angry and disgust. As far as surprise was concerned, only non-psychotic children scored significantly lower (mean = 0.75, SD = 0.3) than controls (mean = 0.96, SD = 0.14) ($p < .001$), whilst psychotic children (mean = 0.86, SD = 0.25) did not differ either from controls or non-psychotic children. As far as sadness was concerned, non-psychotic children (mean = 0.66, SD = 0.3) and psychotic children (mean = 0.68, SD = 0.25) scored lower than controls (mean = 0.92, SD = 0.19) (all *ps* < .05). No significant difference was observed between the two groups of patients. As far as fear was concerned, non-psychotic children (mean = 0.66, SD = 0.3) and psychotic children (mean = 0.62, SD = 0.32) scored lower than controls (mean = 0.87, SD =

0.21) (all *ps* < .05), and no significant difference was observed between the two groups of patients.

In the face-cartoon-matching task, a group*emotion interaction was found ($F(8,388) = 2.53$, $p < .05$, $\eta^2_p = .05$), and post-hoc analyses showed that no significant difference was observed among the three groups (control, non-psychotic children and psychotic children) for happiness, angry, disgust and fear. As far as surprise is concerned, only non-psychotic children scored significantly lower (mean = 0.25, SD = 0.24) than controls (mean = 0.59, SD = 0.27) ($p < .001$), whilst psychotic children (mean = 0.54, SD = 0.61) did not differ either from controls or non-psychotic children. As far as sadness was concerned, only non-psychotic children (mean = 0.45, SD = 0.34) scored lower than controls (mean = 0.73, SD = 0.22) ($p < .05$), whilst psychotic children (mean = 0.46, SD = 0.34) did not differ either from controls or non-psychotic children.

In the face-prosody-matching task, the group*emotion interaction was not significant ($F(8,380) = 1.44$, $p = .17$, $\eta^2_p = .03$).

## 4. Discussion

This study aimed at investigating social cognition, especially emotion perception in a sample of children with 22q11.2DS at high clinical and genetic risk for psychosis compared to neurotypical children (Lattanzi et al., 2018; Tang et al., 2017). For this, children were presented with a protocol composed of three tasks: facial expression recognition task, face-cartoon-matching task and face-prosody-matching task.

The study complemented and confirmed the results obtained by Peyroux and colleagues (2020). Indeed, patients with 22q11.2DS presented with significant impairments in the processing of emotional information compared to healthy controls in recognizing facial expressions, interpreting visually depicted social interactions and emotional prosody through dialogues. This suggests that social cognitive processing in 22q11.2DS is far more complex than just perceiving and recognizing isolated features on faces. Our patients performed even worse in the cartoon and prosody tasks than in the face recognition task. These two tasks are more complex, since they require selecting multiple relevant cues and integrating them with acquired knowledge (Crick & Dodge, 1994) to form a globally coherent image of what occurs and what the

characters' emotional experiences are in each trial. It may be suggested that in attempting to perceive and interpret the nature of social interactions, through either visual or auditory cues, patients with 22q11.2DS have great difficulty and frequently misinterpret what happens. Another, complementary interpretation is that the drop in performance in the two more complex tasks could result from limitations in the processing of multiple target characters. Indeed, both the face-cartoon and the face-prosody-matching tasks involve several characters and also several pieces of secondary information to take into account. The multiplicity of target characters and information could probably exceed the processing capacity of patients and result in decreased performance (Campbell & Swillen, 2005; Morrison et al., 2020). Of most interest was that the IQ level explain only a part of the variance of these differences, suggesting that these patients face genuine social cognitive impairments that are independent from global cognitive efficiency (Badoud et al., 2017; Peyroux et al., 2020).

Another interesting result was that children with 22q11.2DS show smaller emotion perception performance than neurotypical children, but regardless of the presence of psychotic symptoms. These results are in agreement with recent studies conducted on adult populations by Accinni et al. (2022) and Buzzanca et al. (2023) but provide new data in a child population aged 4 to 13 years. These findings suggest that individuals with 22q11.2DS display emotion perception deficits independently of age and the presence of psychotic symptoms.

If we are interested in the perception of specific emotions, the analysis of the proportion of correct responses revealed impairment in recognizing facial expressions as a function of the emotion assessed. Children without psychotic symptoms had difficulties in recognizing surprise and sadness. 22q11.2DS children, regardless of the presence of psychotic symptoms, had difficulties to recognizing fear, like in the study of Campbell et al. (2010). In the face-cartoon-matching task, children without psychotic symptoms had difficulties in recognizing surprise and sadness. Finally, the analysis of the proportion of correct responses did not reveal any differential impairment in recognizing emotional prosody as a function of the emotion assessed; rather, we found a more general impairment in 22q11.2DS compared to controls. All these results are in agreement with certain studies concerning people at high risk of developing a psychosis, which highlight that the difficulties observed do not seem to be linked to a specific type of emotion (Tognin et al., 2020). The total face and prosody emotion recognition performance are not an indicator to psychosis (J. Addington et al., 2012; Allott et al., 2014) whereas it seems that better recognition of fearful and worse recognition of neutral faces is

(Allott et al., 2014). These observations are in line with questions about the origins of the alteration of the emotion perception in schizophrenia (Kohler et al., 2010). A specific emotion deficit has been questioned in relation to a more general impairment of facial processing (Kerr & Neale, 1993; Kohler et al., 2000; Penn et al., 2000; Salem et al., 1996). Among other reasons, impaired emotion perception could be related to the tendency of people with schizophrenia to visually scan for facial features that are not important in the expression of a particular emotion, as shown computerized procedures (Loughland et al., 2002; Sasson et al., 2007).

Our study has some limitations that should be highlighted. First, the type of stimulus used here, namely the sketch of a face, does not resemble real stimuli (such as photographs). Nevertheless, one of reasons for this choice was to optimize our control of all aspects of the stimuli and avoid the typical problems that natural stimuli give rise to (i.e., contrast, saliency, visual complexity). Moreover, the use of drawings minimizes confounds related to facial characteristics that are present in natural photographs, i.e. gender, age, attractiveness, and ethnicity, as well as physical characteristics such as wrinkles and freckles (Peyroux et al., 2020). Another limitation concerns the psychosis screening interview for children used to create our patient groups. It is fairly well established that there are few reliable screening tools, although accurate and early diagnosis is important to treat children as early as possible and improve their future quality of life (McClellan, 2018).

To conclude, emotion perception, taken individually, may therefore not be a useful marker for the development of psychosis (J. Addington et al., 2012; Allott et al., 2014; Van Donkersgoed et al., 2015). In view of the data regarding error patterns in facial emotion perception (Peyroux et al., 2020; Tognin et al., 2020) and the possible link to impaired visual face scanning, future studies in children at high risk of psychosis (e.g., 22q11.2DS) should use eye-tracking to better understand the origin of the difficulties.

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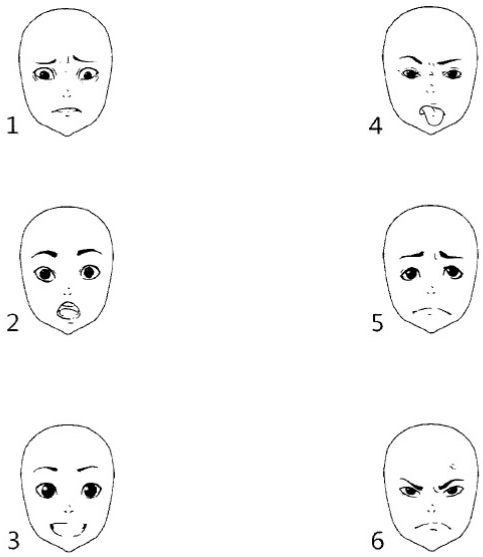


Fig. 1 The six faces that were used in the facial expression recognition task. The same stimuli were also used in the face-cartoon- and the face-prosody-matching tasks as possible responses.

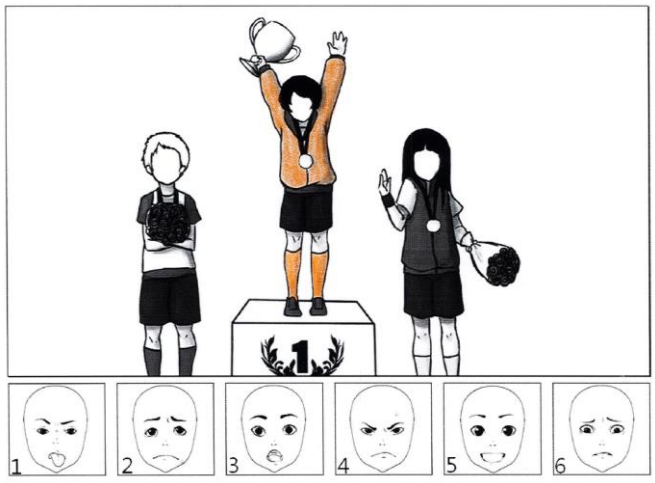


Fig. 2 An example taken from the face-cartoon-matching task. At each new trial participants were requested to attentively look at the picture and choose among the six facial expressions depicted below the one that matched the best the face the unique character in orange clothing would make.

Table 1. Descriptive statistics for age, gender and IQ level for each experimental group.

| **Variable** | **Psychotic children (n = 13)** | **Non-psychotic children (n = 25)** | **Controls (n = 54)** | **Group differences** |
|---|---|---|---|---|
| **% Female** | 23,1% | 46,2% | 50% | $\chi^2(2) = 3.08$, $p = .21$ |
| **Mean (SD) Age in years [range of age]** | 8.85 (2.47) [5.5 – 12.25] | 8.49 (2.31) [5.08 – 13.3] | 8.45 (2.08) [ 4.67 – 13.67] | $F(2,90) = 0.29$, $p = .75$ |
| **IQ measure (assessed with Raven's colored progressive matrices) [range of IQ]** | 91.12 (11.18) [74.5 – 113.5] | 80.73 (13.71) [ 49 – 108.1] | 109.9 (11.03) [74.5 – 133.9] | $F(2,90) = 56.58$, $p < .001$ |

# DISCUSSION

Dans cette partie seront rassemblés les principaux résultats des études menées lors de cette thèse dont l'objectif était de mieux comprendre les prodromes comportementaux à l'apparition des symptômes psychotiques chez l'enfant, en prenant le modèle génétique de la délétion 22q11.2. Nous tenterons de mettre en avant comment nos résultats contribuent à une meilleure compréhension des facteurs impliqués dans l'apparition de ces symptômes, en faisant le lien avec la littérature existante. Pour rappel, nous avons dans un premier temps développé une nouvelle échelle de dépistage des symptômes psychotiques chez l'enfant à partir de 4 ans et étudié le développement des différents symptômes selon les groupes d'enfants étudiés (neurotypiques, porteurs d'un trouble du neurodéveloppement sans symptômes psychotiques et porteurs d'un trouble du neurodéveloppement avec symptômes psychotiques) (Étude 1). Par la suite, et à la lumière de la littérature qui questionne régulièrement les liens entre symptômes psychotiques voire schizophrénie et une perception atypique du regard, nous avons réalisé une revue de la littérature sur cette thématique. Mieux appréhender la perception et la détection de la direction du regard dans le champ du normal nous permet en tant que chercheurs de mieux cerner les atypies qui seraient liées à un trouble ou une pathologie. Dans la lignée de cette revue narrative de littérature, nous nous sommes intéressés au déroulement temporel de la perception du regard chez des individus neurotypiques (Étude 2). Ces premiers résultats suggéraient que chez tout individu qui est confronté à un visage, les yeux étaient le premier élément facial à être détecté sans que l'information sur la direction du regard ne soit immédiatement disponible. Le visage qui crée un contexte facial était le second élément à être perçu, et favorisait ainsi le traitement de la direction du regard. Enfin, il apparaissait que le traitement du regard direct et du regard détourné se faisait selon des processus différents, entraînant un déroulement temporel spécifique pour chaque direction du regard. L'hypothèse attentionnelle sous-jacente a été soulevée pour tenter d'expliquer ces différents processus de traitement de l'information. Dans la continuité de ces premiers travaux, et sur la base de la littérature établissant un lien entre perception du regard et de l'émotion, nous avons mis en place un protocole basé sur une mesure comportementale, qui est le reflet de la capture attentionnelle vis-à-vis d'un stimulus (Etude 3). Cette étude visait ainsi à mieux comprendre la réponse comportementale d'enfants à haut risque de psychose (porteurs d'un 22q11.2DS) face à la perception d'un regard émotionnel ou non. Les résultats ont confirmé que les yeux sont un stimulus particulier, mais il est apparu que le traitement atypique de l'information provenait principalement d'un effet de l'émotion associé au regard. Les relations étroites et généralisables entre les capacités attentionnelles et inhibitrices, et la perception du regard émotionnel, laissaient penser l'existence d'un marqueur important présent dans la population générale, mais sur-exprimé dans les populations à risque

de symptômes psychotiques comme dans le 22q11.2DS. Si le traitement atypique de l'information provient de l'émotion spécifiquement, le rôle plus précis de la perception émotionnelle se devait d'être approfondi. La suite de ce travail de thèse a consisté à étudier les processus de perception émotionnelle chez des enfants présentant un 22q11.2DS, donc à haut risque de développer des symptômes psychotiques (Etude 4). Afin d'affiner nos résultats, l'Étude 5 s'est intéressée plus spécifiquement à l'impact de la présence de symptômes psychotiques sur les processus de perception émotionnelle, en distinguant deux groupes d'enfants porteurs d'un 22q11.2DS (présentant des symptômes psychotiques ou non). En guise de conclusion, nous présenterons certaines des problématiques auxquelles sont confrontées les études sur la perception du regard dans une population à haut risque de psychose.

# I. L'apport des maladies rares en pédopsychiatrie

## A – Les difficultés de diagnostic de la schizophrénie à début très précoce

Rappelons que les études s'accordent sur une prévalence d'environ 0.03% de la population générale pour la schizophrénie à début très précoce (c'est-à-dire avant l'âge de 13 ans (Dumas & Bonnot, 2013). Toutefois, ces chiffres sont probablement sous-estimés en raison de la difficulté à poser ce diagnostic, en particulier chez le jeune enfant. En effet, la présence de symptômes psychotiques chez des enfants tout venant n'est pas si rare que cela (jusqu'à 5%) (Kelleher et al., 2012; Kelleher & Cannon, 2011), et peut complexifier le diagnostic différentiel d'autant plus que les évaluations cliniques standardisées font défaut ou se basent en partie sur l'avis des enfants (Jones et al., 2015). Il est vrai que des études ont démontré que les enfants qui vers l'âge de 11 ans signalaient des symptômes psychotiques avaient 5 à 16 fois plus de risques de développer un trouble du spectre de la schizophrénie à l'âge adulte (Poulton et al., 2000). Toutefois, les enfants sont-ils tous conscients de leurs symptômes ? Parviennent-ils tous à exprimer leurs symptômes lorsque parfois ces derniers sont minimisés par l'entourage faute de connaissances ? Prenons l'exemple de Justine[3], 7 ans, qui lors d'une consultation sans ses parents exprime le fait de voir des ombres le soir avant de se coucher et d'entendre des craquements. Elle poursuit ses propos en expliquant que ses parents lui ont dit qu'il s'agissait des arbres qui bougeaient avec le vent et de probables souris dans le grenier (propos confirmés par les parents par la suite). Quelques années plus tard, Justine développera d'autres symptômes tels que des hallucinations acoustico-verbales qui dictent ses actions selon ses explications. Bien que cela ne soit pas aisé pour des parents, et dans la mesure où il est difficile de vérifier les informations décrites, il est plus sûr de croire l'enfant ou de lui laisser le bénéfice du doute pour lui permettre de se sentir écouté et d'être plus disposé à se confier (Roy, 2008).

[3] Par soucis de confidentialité, le prénom a été modifié.

## B – Une meilleure compréhension des symptômes psychotiques de l'enfant grâce aux maladies rares

Aborder les concepts de troubles psychiatriques par le prisme des maladies rares permet d'identifier et de diagnostiquer des symptômes, retrouvés en pédopsychiatrie générale, par le biais de maladies dont l'origine peut être connue et dont les caractéristiques neurodéveloppementales sont bien établies (Nguengang Wakap et al., 2020). Ainsi, l'étude des maladies rares, comme par exemple la délétion 22q11.2, est essentielle pour la recherche clinique, puisqu'elle permet d'avoir accès à une population spécifique connue pour étudier les causes, les mécanismes sous-jacents d'affections particulières. A travers les différentes études menées au cours de cette thèse, l'apport de l'étude des maladies rares apparaît assez clairement. En effet, dans l'étude 1, la participation d'enfants porteurs d'un 22q11.2DS dont on sait que le risque accru de développer des symptômes psychotiques à l'adolescence est accru (Monks et al., 2014), a permis d'étoffer de manière significative les groupes d'enfants porteurs d'un Trouble du Neurodéveloppement. Cette étude a notamment permis de développer une nouvelle échelle de dépistage des symptômes psychotiques précoces chez l'enfant (EPSy) et d'investiguer différentes symptomatologies en fonction du groupe d'appartenance de l'enfant (neurotypique, porteur d'un trouble du neurodéveloppement sans symptômes psychotiques, porteur d'un trouble du neurodéveloppement avec symptômes psychotiques). Les résultats ont permis de mettre en exergue que les symptômes bien que présents chez tous les enfants, s'expriment différemment en fonction du groupe d'appartenance de l'enfant, positionnant la réflexion dans une approche dimensionnelle plutôt que catégorielle. Les symptômes de méfiance se sont révélés être présents dans les trois groupes, aussi bien à l'âge de 2 ans qu'à l'âge actuel. Bien que les délires de persécution et la méfiance ne soient pas toujours faciles à distinguer de la réalité chez les enfants et les adolescents (Sikich, 2013), nos résultats ont montré une distinction fiable entre les trois groupes étudiés avec la présence de symptômes très prégnants chez les enfants psychotiques, tandis qu'ils étaient moins présents chez les enfants non psychotiques et encore moins chez les enfants neurotypiques (Schultze-Lutter et al., 2022; Zhou et al., 2018). Globalement, les symptômes de méfiance se sont révélés être un indicateur important et très précoce (dès 2 ans) de la psychose, bien que pris unitairement, ce symptôme n'est pas suffisamment robuste (Preti et al., 2012; Wong et al., 2014). La combinaison avec des symptômes de désorganisation et d'hallucinations semble alors être un point de vigilance à l'âge actuel d'évaluation de l'enfant (Giannitelli et al., 2020). Il semble en revanche qu'à un

âge très précoce (2 ans), bien que la désorganisation soit associée à la schizophrénie précoce (Nestsiarovich et al., 2017), ce symptôme soit à considérer plutôt comme un symptôme structurel global d'un trouble neurodéveloppemental. Ces données appuient les réflexions menées quant à la nécessité d'une approche dimensionnelle de la psychiatrie (Gaebel et al., 2020). Les systèmes de classification basés sur une approche catégorielle permettent d'attribuer en fonction d'un nombre prédéfini de symptômes un diagnostic (Parnas, 2015). Bien qu'elle ait des avantages, ce type de classification est malgré tout associée à diverses limites, notamment une grande hétérogénéité intra-catégorie, des comorbidités inter-catégories, ainsi que des difficultés à représenter des symptomatologies frustres (Krueger & Bezdjian, 2009). Dans une approche dimensionnelle, le focus est envisagé sur la gravité d'un symptôme ou le degré de perturbation d'une fonction psychologique spécifique d'un point de vue quantitatif, permettant ainsi une approche du normal au pathologique selon un continuum (van Os et al., 2009). Bien que la complexité de ce type de classification ait été soulevée (Gaebel et al., 2020) d'un point de vue clinique, et au regard des résultats de notre étude 1, il semble important de mettre l'accent sur ce type d'approche dans le but d'affiner la compréhension des symptomatologies en pédopsychiatrie et en psychiatrie.

Dans les études chez l'adulte, les personnes présentant un sentiment de méfiance envers les autres voire de persécution, telle que décrit dans la schizophrénie et par extension dans la schizophrénie à début très précoce, sont plus susceptibles de détecter la menace dans les signaux sociaux véhiculés par les autres (Blakemore et al., 2003). Cette sur-détection de la menace aussi nommée biais attentionnel à la menace semble induite par une capacité plus élevée à focaliser son attention sur la cible (Prochwicz & Kłosowska, 2017). Les études sur la perception du regard et des émotions chez des enfants porteurs d'un 22q11.2DS, définis comme étant à haut risque de psychose, permettront de discuter d'un lien potentiel entre symptômes de méfiance, biais attentionnel, et signaux sociaux tels que le regard émotionnel.

## II. L’attention au service de la cognition sociale

La revue narrative de littérature présentée dans le cadre de cette thèse a suggéré que les visages et plus spécifiquement les yeux sont préférentiellement détectés dès les premiers jours de vie en raison de leurs propriétés structurelles qui confèrent un biais attentionnel à leur égard (Simion et al., 2001, 2002). Par ailleurs, l’hypothèse d’une priorité de traitement accordée au regard direct en raison d’une saillance perceptive a été évoquée. L’étude 2 qui s’est intéressée plus spécifiquement au déroulement temporel de la perception du regard suggère en effet cette priorité de traitement face à un regard direct associée à une difficulté à se désengager par la suite de ce contact mutuel (Burra & Kerzel, 2021). Il est apparu par la suite que le traitement atypique d’un regard émotionnel proviendrait principalement d’un effet de l’émotion (Etude 3), ce qui questionne le rôle spécifique de l’attention sur cette perception.

### A – Attention et regard : une interdépendance à investiguer

L’attention sert à prioriser les informations qui ont une valeur de survie, en allouant de préférence des ressources aux stimuli qui indiquent une menace ou une récompense, tels que le regard (Bradley, 2009). Une des fonctions essentielles du système cognitif est d’analyser les intentions dans les interactions sociales. Pour cela, nous analysons constamment le comportement des autres afin de pouvoir réagir de manière appropriée, en portant notre attention sur le visage et les yeux. Cette analyse semblerait se faire selon un continuum permettant de distinguer si notre interlocuteur nous regarde ou s’il regarde ailleurs (Etude 2). Les résultats de cette étude ont mis en évidence que les yeux étaient le premier élément facial à être détecté lorsque nous percevons un visage, mais que l’information concernant la direction du regard n’était pas disponible immédiatement. Il existerait ainsi un mécanisme précoce d’orientation spatiale automatique (Benso et al., 1998; Müller & Findlay, 1988), permettant de capter la région des yeux (Burra & Kerzel, 2021). Pour juger l’orientation du regard de l’autre, il serait par la suite nécessaire de traiter le contexte facial, c’est-à-dire les autres traits du visage. Le traitement d’un regard direct (dirigé vers nous) ou d’un regard détourné (regardant ailleurs) semblerait ainsi se faire selon un processus temporel défini, entres autres, par des capacités

attentionnelles. Le traitement d'un regard direct s'effectuerait très rapidement et perdurerait dans le temps, en raison de sa saillance perceptive (Babinet et al., 2022). Cette saillance engendrerait une focalisation attentionnelle rapide (Parr & Friston, 2019) mais qui entraînerait également une difficulté à désengager l'attention d'un contact mutuel (Burra & Kerzel, 2021). La perception d'un regard détourné, ne mettrait pas en exergue les mêmes capacités attentionnelles. Le traitement de cette information serait déclenché par un déplacement du focus attentionnel vers la direction dans laquelle les yeux regardent (Frischen et al., 2007), puis serait suivi d'un désengagement attentionnel coïncidant à la prise de conscience que nous ne sommes pas la cible de l'attention de l'interlocuteur (Wang et al., 2019). L'ensemble de ces mécanismes attentionnels semblent toutefois valides lorsque le stimulus œil est présenté seul (Burra & Kerzel, 2021). Mais qu'en est-il lors de la perception d'une scène visuelle ?

Confrontés à une scène visuelle en l'absence d'une tâche ou d'une consigne prédéfinie, nous nous tournons généralement vers des objets ayant une importance sociale, à savoir les individus, leurs visages et surtout leurs yeux (Emery, 2000; Yarbus, 1967). En revanche, lorsqu'il est nécessaire de sélectionner des informations pertinentes de l'environnement pour inférer un jugement sur le regard, nous devons répartir notre attention différemment, entraînant une division de la focalisation attentionnelle sur différentes cibles importantes (Sussman et al., 2013).

### B – Quand l'émotion s'en mêle !

L'Homme est le plus émotif de tous les animaux selon Donald Hebb (1950), laissant supposer que le degré de perception émotionnelle augmente à travers les espèces, notamment grâce au développement de systèmes nerveux plus complexes. En parallèle de son rôle important dans la perception de la direction du regard, la région oculaire véhicule des informations nécessaires à la reconnaissance des émotions (Bindemann et al., 2008; Itier & Batty, 2009). L'émotion remplissant une fonction adaptative, il semble assez évident que cela complexifiera le traitement de l'information (Dalmaso et al., 2020). Toutefois, les résultats obtenus chez des enfants neurotypiques (Etude 3) n'ont pas permis de mettre en évidence un traitement de l'information différent entre perception d'un regard direct non émotionnel et émotionnel. Cette absence de résultats peut provenir d'un manque de sensibilité de

l'expérience. Par ailleurs, des recherches antérieures ont montré que la perception d'une émotion est facilitée (Adams & Kleck, 2003, 2005) lorsque la direction du regard correspond à l'intention comportementale sous-jacente (approche / évitement) communiquée par l'expression émotionnelle. Dans l'expérience proposée au cours de l'Etude 3, les deux émotions proposées (colère et tristesse) étaient véhiculées par des regards directs. Or, les visages exprimant de la colère sont détectés plus rapidement et perçus avec une plus grande intensité lorsque le regard de l'interlocuteur est dirigé vers l'observateur (Sander et al., 2007), tandis qu'un regard détourné améliore plutôt la perception de visages craintifs (Rigato et al., 2013) et de visages tristes (Adams & Kleck, 2003). Nous pouvons ainsi supposer que la réponse comportementale des enfants neurotypiques ait été impactée par ce biais de procédure entraînant l'absence de résultats citée précédemment.

Le traitement et la compréhension des informations sociales, et par conséquent émotionnelles, nécessitent également la collecte et le traitement d'indices au-delà des expressions faciales, telles que les informations posturales et vocales présentes dans les interactions sociales ou la prosodie. Les résultats de l'Etude 4 ont mis en évidence de meilleures performances chez des enfants neurotypiques dans une tâche d'attribution de l'émotion sur visages seuls comparé à une tâche d'attribution de l'émotion en contexte et à une tâche d'attribution de l'émotion via la prosodie. Etant donné la nécessité de sélectionner des informations pertinentes de l'environnement pour attribuer l'émotion adéquate en fonction du contexte ou de la voix, la baisse de performance pourrait provenir de la stratégie de division de la focalisation attentionnelle sur différentes cibles importantes (Sussman et al., 2013).

### C – Quand le cerveau se développe différemment !

Etant donné l'importance de la perception du regard et des émotions dans les interactions sociales (Emery, 2000), il n'est pas surprenant que dans certains troubles psychiatriques, tels que la schizophrénie ou les personnes à haut risque de psychose, les personnes présentent des troubles de la cognition sociale (Cañadas & Lupiáñez, 2012; Morel et al., 2018). Les caractéristiques de la schizophrénie à début très précoce peuvent se retrouver dans différents troubles du neurodéveloppement d'origine génétique tels que la délétion 22q11.2 (Kendhari et al., 2016). Les résultats de l'Etude 3 ont mis en évidence que l'effet de l'émotion rapportée dans la littérature en population générale (Adams & Franklin, 2009; Adams

& Kleck, 2003, 2005) semblerait plus important chez des enfants porteurs d'un 22q11.2DS. Il est bien établi que ces enfants présentent des difficultés attentionnelles plus marquées notamment en termes de filtrage attentionnel (Linton et al., 2021). Les difficultés de perception émotionnelle observées dans l'Etude 3 pourraient ainsi provenir d'une plus grande captation attentionnelle associée à un désengagement attentionnel ultérieur plus complexe (Kalanthroff et al., 2017) voire à des difficultés d'inhibition. En effet, si en lien avec le sentiment de méfiance, le regard émotionnel est une source de motivation plus importante pour les enfants porteurs d'un 22q11.2DS que les neurotypiques (De Tommaso & Turatto, 2022), il est probable que cela génère la cascade attentionnelle décrite ci-dessus.

Bien que des difficultés d'attribution de l'émotion en contexte aient été mis en évidence chez des enfants neurotypiques, une baisse de performance plus marquée a été observée dans une population d'enfants présentant un 22q11.2DS (Etude 4). Lors de la perception d'une scène sociale chez ces enfants, les difficultés d'attribution de l'émotion à un personnage pourrait ainsi provenir d'une double difficulté : (i) difficulté de balayage visuel pour détecter les informations cibles nécessaire à la bonne compréhension de l'émotion (McCabe et al., 2016), (ii) difficulté de perception émotionnelle spécifique mise en évidence dans l'Etude 3. La majeur partie des études sur l'impact des symptômes psychotiques sur la cognition sociale laissent suggérer qu'il n'existe pas de corrélations entre ces ressources en cognition sociale et le risque de psychose (Tang et al., 2017; Yi et al., 2015). Cependant, les études existantes se contredisent régulièrement. Certaines expliquent un déficit de reconnaissance des émotions faciales plus marqués chez les personnes avec 22q11.2DS et trouble psychotique (Weinberger et al., 2016, 2018), pouvant ainsi être un indicateur de certains symptômes de la psychose (Jalbrzikowski et al., 2012). D'autres études très récentes (Accinni et al., 2022; Buzzanca et al., 2023) suggèrent un déficit global de cognition sociale chez des adultes porteurs d'un 22q11.2DS, tel qu'observé dans la schizophrénie, mais quelque que soit leur symptomatologie psychotique. Des résultats similaires ont été obtenus dans l'Etude 5 menée au cours de cette thèse, permettant de mettre en évidence un trouble de la perception émotionnelle chez des enfants porteurs d'un 22q11.2DS, indépendamment de leur symptomatologie psychotique. La perception altérée des émotions ne semble donc pas à elle seule un indicateur fiable pour le développement de symptômes psychotiques (Tognin et al., 2020). En revanche, la surinterprétation de certaines émotions telles que la peur dans un contexte de sentiment de paranoïa (Pinkham et al., 2011, 2016), de symptômes de méfiance, par captation attentionnelle plus importante (De Tommaso

& Turatto, 2022), pourrait être une piste indicative voire un marqueur de la présence de symptômes psychotiques précoces.

## III. Qu'en est-il des réseaux neuronaux qui sous-tendent cette perception du regard et des émotions ?

Bien que des recherches supplémentaires soient nécessaires, il semblerait que la détection du regard et de sa direction soit soutenue par un système spécialisé (voir Figure 2 in Babinet et al. (2022)) combinant (i) des voies de traitement de bas niveau, à savoir la voie extragéniculée (c'est-à-dire le colliculus supérieur, le pulvinar et l'amygdale ; Kawashima et al., 1999; Senju & Johnson, 2009) et des sections de la voie géniculostriée (c'est-à-dire le cortex visuel primaire), (ii) et des structures temporales dont le gyrus fusiforme qui assure le traitement multisensoriel (Grosbras et al., 2005; Peyroux et al., 2020) et le Sulcus Temporal Supérieur (STS) qui permet de représenter la direction du regard d'une personne (George et al., 2001; Grosbras et al., 2005; Hoffman & Haxby, 2000; Itier & Batty, 2009; Perrett et al., 1990). Il semblerait que le contraste de luminance dérivé des aspects spatiaux et topographiques du visage déclenche une activité dans le cortex strié liée à la direction du regard. Cette activité contribue probablement à la construction d'une représentation de la direction du regard dans le STS postérieur (STSp) contenant des informations rétinotopiques et permet ainsi la construction ultérieure d'une représentation dynamique de la direction et des mouvements du regard (Babinet et al., 2022). Ces informations peuvent également permettre la construction d'une représentation invariante du regard au sein du STS antérieur (STSa) (Carlin & Calder, 2013; Cheng et al., 2018). D'autres structures corticales semblent impliquées, mais leur rôle est moins clair. Ce sont (iii) des zones pariétales telles que le sulcus intrapariétal et la jonction temporo-pariétale qui peuvent aider à allouer les ressources attentionnelles (Carlin & Calder, 2013; George et al., 2001; Grosbras et al., 2005; von dem Hagen et al., 2014) et (iv) les zones frontales qui pourraient être impliquées dans le codage des informations émotionnelles véhiculées par le regard d'une personne ou dans la promotion de l'attention conjointe (Carlin & Calder, 2013; Itier & Batty, 2009).

Certaines études dans le domaine de la schizophrénie suggèrent que les patients présentant des signes de paranoïa et des symptômes négatifs sont plus susceptible de dire que quelqu'un les regardait même si cela n'est pas réellement le cas (Abbott et al., 2018; Tso et al., 2012). De récentes études en neuroimagerie soulignent une réduction de l'activation dans le STSp lors d'une tâche de reconnaissance des émotions (Martínez et al., 2022). Au-delà de l'explication que cela peut apporter concernant les performances en reconnaissance des émotions faciales, cette réduction de l'activation dans le STSp pourrait également soutenir le biais de perception du regard retrouvé dans la schizophrénie (Tso et al., 2012). Martínez et ses collègues (2022) suggèrent différents niveaux d'atteinte, tant au niveau du cortex visuel primaire, que du pulvinar, que du STS. Plus précisément, il semblerait que le réseau spécialisé dans la perception du regard évoqué dans notre revue de littérature soit, dans le cadre de la schizophrénie, impacté à différents niveaux selon une cascade neuronale (Martínez et al., 2022).

# IV. Etudier la perception du regard et des émotions comme outil diagnostique, vers de nouvelles approches

Les chercheurs en psychologie, sciences cognitives et neurosciences consacrent de l'énergie et du temps pour développer des outils permettant de dépister précocement des symptômes psychotiques dans une recherche de prise en charge précoce en réhabilitation psychosociale. A l'heure des nouvelles technologies, il serait idéaliste d'imaginer un outil de dépistage à l'aide par exemple de l'eye-tracking. En effet, cette mesure permet la détection de la position de l'œil et de la direction du regard avec une haute résolution temporelle et reflète donc mieux l'exploration attentionnelle naturelle (König et al., 2016). Toutefois, il semble important de souligner que l'utilisation de ce type d'outil et les résultats qui pourraient en découler sont confrontés, comme les mesures en neuropsychologie expérimentale, à certains facteurs limitants. Dans le champ de la schizophrénie, rappelons que des résultats contradictoires ont été retrouvés dans les capacités de perception du regard (Franck et al., 1998, 2002; Palmer et al., 2018; Seymour et al., 2016; Tso et al., 2012). Ces disparités pourraient être dues, selon plusieurs auteurs (Babinet et al., 2022; Seymour et al., 2017), à un biais de réponse en lien avec la nature de la tâche et les instructions données aux participants (Macmillan & Creelman, 2004).

Les mêmes observations sont retrouvées dans les études qui s'intéressent au 22q11.2DS, à leurs compétences sociales et aux liens potentiels avec des symptômes psychotiques précoces. La plupart des études menées en eye-tracking ont utilisé des stimuli statiques tels que des photos et sont basées sur la labélisation de l'émotion exprimée par la personne en photo (Campbell et al., 2010; Glaser et al., 2010; McCabe et al., 2011; McCabe et al., 2013). Deux études ont étudié l'exploration visuelle de scènes sociales à travers des stimuli dynamiques (Dubourg et al., 2023; Franchini et al., 2016), sans instructions particulières au préalable. Enfin, les études menées dans le cadre de cette thèse ainsi que l'étude menée par Peyroux et collaborateurs (2020) ont utilisé des stimuli de type dessins aux traits pour contrôler le biais introduit par des stimuli naturels. Au regard de l'hétérogénéité des stimuli utilisés ainsi que des tâches proposées et des résultats hétérogènes retrouvés, il semble prématuré d'envisager le développement d'un outil de dépistage des symptômes psychotiques précoces utilisant par exemple l'eye-tracking. Toutefois, fort de l'expérience dans d'autres domaines notamment en addictologie, de futures études pourraient s'intéresser à la combinaison entre eye-tracking et réalité virtuelle (Callea, 2021).

# V. Limites et perspectives

L'ensemble des études menées dans ce travail de thèse comporte des limites qu'il convient de souligner et de discuter. Premièrement, s'intéresser à l'apparition de symptômes psychotiques chez des enfants à partir de 4 ans présente un facteur limitant qu'est la faible prévalence connue de la Schizophrénie à début très précoce (ou *Chidhood Onset Schizophrenia*, COS) (Driver et al., 2013). Au-delà de cette prévalence limitante, il convient de questionner la difficulté du diagnostic en pédopsychiatrie dans une dimension catégorielle. En psychiatrie infanto-juvénile, un diagnostic stable semble difficile à poser (De Becker et al., 2015). Le propre de chaque être humain est d'évoluer, et poser un diagnostic dans une perspective de processus développemental en pleine évolution notamment chez les enfants semblent parfois trop restrictif. En revanche, comme cela a pu être évoqué dans l'Etude 1 de cette thèse, considérer une approche dimensionnelle semblerait intéressante dans le sens où les troubles psychiatriques existent sur un continuum de symptômes et de sévérité. Une approche

dimensionnelle permettrait ainsi de mieux capturer la diversité et les nuances des présentations cliniques (De Becker et al., 2015; Gaebel et al., 2020). Une deuxième limite des études présentées dans cette thèse concerne le type de stimulus utilisé dans les Etudes 2 à 5, à savoir un dessin de regard et/ou de visage, qui ne ressemble pas à des stimuli réels, comme cela pourrait être le cas avec des photographies. Néanmoins, l'une des raisons de ce choix était d'optimiser le contrôle de tous les aspects des stimuli et d'éviter des problèmes typiques que peuvent générer des stimuli naturels (c'est-à-dire, le contraste, la saillance, la complexité visuelle). De plus, l'utilisation de dessins minimise les confusions liées aux caractéristiques faciales présentes dans les photographies naturelles, à savoir le sexe, l'âge, l'origine ethnique. Troisièmement, plusieurs études ont suggéré que la reconnaissance altérée de l'expression faciale dans le 22q11.2DS pourrait être due à un balayage visuel désordonné (Campbell et al., 2010; Franchini et al., 2016; Glaser et al., 2010) ou à des déficits dans les processus perceptuels (McCabe et al., 2016). Il est difficile dans les études 4 et 5 présentées dans cette thèse de démêler ces deux possibilités car d'une part le premier peut conditionner l'efficacité du second et vice-versa, et d'autre part aucune technique de suivi oculaire n'a été utilisée. Dans cette perspective, il pourrait être utile dans de futures études de coupler des mesures comportementales et des mesures d'eye-tracking. Enfin, une quatrième limite concerne l'outil de dépistage utilisé pour créer les groupes de patients et différencier ceux présentant des symptômes psychotiques de ceux n'en ayant pas. Il est assez bien établi qu'il existe peu d'outils de dépistage fiables bien que cela soit nécessaire pour une prise en charge précoce et adaptée (McClellan, 2018). Dans une optique d'approche dimensionnelle, l'utilisation de la nouvelle échelle EPSy pourrait être envisagée dans ce type d'études investiguant les liens entre troubles de la cognition sociale et présence de symptômes psychotiques.

# VI. Conclusion

Ce travail de thèse a exploré les signes précurseurs à l'apparition de symptômes psychotiques chez les enfants en prenant comme modèle neurodéveloppemental d'origine génétique la délétion 22q11.2. En utilisant différentes méthodes, nous avons montré l'importance d'une évaluation précoce du comportement chez ces enfants grâce à des

marqueurs spécifiques tels que la méfiance et la désorganisation, bien que les hallucinations restent un point essentiel. D'autre part, nous avons montré que le traitement atypique du regard semble provenir principalement d'un effet de l'émotion sous-tendus par des processus attentionnels et exécutifs. En ce sens, nous avons mis en évidence que les capacités inhibitrices jouaient un rôle clé dans la capacité à détecter les émotions à travers le regard. Enfin, nous nous sommes intéressés à la perception émotionnelle de manière plus large, que ce soit en contexte social ou à travers la voix (prosodie), afin d'étudier l'impact de la présence de symptômes psychotiques sur ces performances. Bien que nos résultats aient montré une déficience globale de perception émotionnelle chez les enfants à haut risque de psychose (délétion 22q11.2), peu importe leur symptomatologie actuelle, il apparaît que le focus des futures études devrait se tourner davantage sur des biais de reconnaissance plutôt que des déficits.

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