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Original article

Neural activations during cognitive and affective theory of mind processing in healthy adults with a family history of alcohol use disorder

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ABSTRACT

Background. Social cognition impairments are a common feature of Alcohol Use Disorders (AUD). However, it remains unclear whether these impairments are solely the consequence of chronic alcohol consumption or whether they could be a marker of vulnerability.

Methods. The present study implemented a family history approach to address this question for a key process of social cognition: theory of mind (ToM). Thirty healthy adults with a family history of AUD (FH+) and 30 healthy adults with a negative family history of AUD (FH-), matched for age, sex, and education level, underwent an fMRI cartoon-vignette paradigm assessing cognitive and affective ToM. Participants also completed questionnaires evaluating anxiety, depressive symptoms, childhood trauma, and alexithymia.

Results. Results indicated that FH+ individuals differed from FH- individuals on affective but not cognitive ToM processing, at both the behavioral and neural levels. At the behavioral level, the FH+ group had lower response accuracy for affective ToM compared with the FH- group. At the neural level, the FH+ group had higher brain activations in the left insula and inferior frontal cortex during affective ToM processing. These activations remained significant when controlling for depressive symptoms, anxiety, and childhood trauma.

Conclusions. These findings highlight difficulties during affective ToM processing among first-degree relatives of AUD patients, supporting the idea that some of the impairments exhibited by these patients may already be present before the onset of AUD and may be considered a marker of vulnerability.

Key words: alcohol use disorder; social cognition; theory of mind; family history; fMRI

Introduction

Social cognition refers to the cognitive processes underlying the comprehension of the behaviors of others in a social context, and encompasses the perception and interpretation of social cues, as well as the ensuing responses to these cues (Frith, 2008; Happé, Cook, & Bird, 2017). A growing body of research has highlighted impairments in various social cognition processes in individuals with Alcohol Use Disorders (AUD), at both the neural and behavioral levels (Bora & Zorlu, 2017; Le Berre, 2019). For instance, individuals with AUD have demonstrated deficits in empathy and facial emotion recognition compared to healthy controls (Grynberg, Maurage, & Nandrino, 2017; Kumar, Skrzynski, & Creswell, 2022a; Maurage et al., 2021). On the neural level, these deficits were associated with structural and functional changes in several brain regions, notably the medial prefrontal cortex, the inferior frontal cortex, the insula, and the amygdala (Marinkovic et al., 2009; Trick, Kempton, Williams, & Duka, 2014). A deeper understanding of social cognition deficits in AUD is warranted given that they are associated with a range of functional consequences of AUD, such as more frequent interpersonal problems and higher relapse rates (Lewis, Price, Garcia, & Nixon, 2019; Rupp, Derntl, Osthaus, Kemmler, & Fleischhacker, 2017).

A core aspect of social cognition is theory of mind (ToM), the ability to attribute mental states, thereby allowing individuals to understand and predict other people's reactions and behaviors (Premack & Woodruff, 1978). It is common to distinguish between two ToM components: affective ToM (i.e., ability to infer emotional mental states), and cognitive ToM (i.e., ability to infer non-emotional mental states such as intentions and beliefs) (Abu-Akel & Shamay-Tsoory, 2011).

In AUD, ToM impairments have been found with tasks targeting both, affective and cognitive ToM (Pabst, Gautier, & Maurage, 2022). However, some studies have reported dissociations. For instance, Nandrino et al. (2014) found that AUD patients performed worse

than controls on the *Reading the Mind in the Eyes Test* (Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001), a task which is commonly considered to assess affective ToM, while no significant intergroup difference was found on a task assessing cognitive ToM. In the same line, Maurage et al. (2016) found preserved performances for cognitive ToM and impaired performances for affective ToM among recently detoxified AUD patients, using the *Movie for the Assessment of Social Cognition* (Dziobek et al., 2006). Altered affective processing has thus been described as a core feature of AUD and may be more severely impaired than the inference of non emotional mental states (Le Berre, 2019). Affective and cognitive ToM impairments have been associated with moderate to large effect sizes in meta-analyses and entail tangible repercussions (Bora & Zorlu, 2017; Onuoha, Quintana, Lyvers, & Guastella, 2016). Their presence considerably increases interpersonal problems and reduces social connectedness (Quednow, 2020). Considering the tight link between social support and drinking outcomes, ToM impairments likely favor problematic drinking behavior and may impede long-term abstinence (Robinson, Fokas, & Witkiewitz, 2018).

However, as the chronology of these ToM impairments in AUD is still not clearly established (Le Berre, 2019), we do not yet know whether these impairments solely reflect the impact of alcohol toxicity on brain functioning, or whether they co-occur with or even precede the onset of AUD (Kumar, Skrzynski, & Creswell, 2022b). These two possibilities are not mutually exclusive: ToM impairments may be a consequence of AUD but also a risk factor, with prior ToM difficulties being exacerbated by subsequent alcohol consumption.

Adopting a family history (FH) approach can bring new insights on this question (Nurnberger et al., 2004; Robbins, Gillan, Smith, de Wit, & Ersche, 2012). A FH of AUD is known to considerably increase an individual's likelihood of developing this disorder (Prescott et al., 2005; Rangaswamy et al., 2007). This risk is commonly considered to be the reflection of shared genetic and environmental factors within a family (Stoltenberg, Mudd,

Blow, & Hill, 1998). Hence, more frequent alcohol-related problems and higher AUD prevalence rates have been found in individuals with a positive FH of AUD (FH+), compared to those with a negative FH of AUD (FH-) (Hill & O'Brien, 2015; Kosty et al., 2020).

Regarding the mechanisms which might drive this increased vulnerability for AUD, a large body of research indicates that FH+ individuals demonstrate differences in psychological functioning and altered cognitive performances compared to FH- individuals in various domains such as executive functions (Gierski et al., 2013; Saunders et al., 2008), working memory (Mackiewicz Seghete, Cservenka, Herting, & Nagel, 2013; Spadoni, Norman, Schweinsburg, & Tapert, 2008), impulsivity (Khemiri, Franck, & Jayaram-Lindström, 2022), and reward processing (Yarosh et al., 2014). These alterations were found to be predictive of subsequent AUD development in FH+ individuals (Hill, Steinhauer, Locke-Wellman, & Ulrich, 2009; Nigg et al., 2006) and have been consistently linked to neurobiological specificities (see Cservenka, 2016, for a review), such as gray-matter volume (Dager et al., 2015), white-matter microstructure (Acheson et al., 2014), or brain functioning (Amico et al., 2020).

However, there is a dearth of studies to investigate social cognition processes as vulnerability factors for AUD, especially ToM abilities (Kumar et al., 2022b), despite their major contribution to efficient social functioning (Quednow, 2020). This is even more surprising, given that the few FH studies to have explored social cognition processes have highlighted differences between FH+ and FH- individuals (Cservenka, 2016; Khemiri et al., 2022). Indeed, FH+ individuals have been shown to have reduced gray-matter volume in the amygdala, a region involved in emotional learning and social appraisal (Hill et al., 2001, 2013). In addition, at the neurofunctional level, FH+ adolescents and young adults were found to exhibit blunted brain activation in the superior temporal cortex during the processing of emotional facial expressions during a Go/No-go task (Cservenka, Fair, & Nagel, 2014), in the

amygdala during an emotion-matching task (Glahn, Lovallo, & Fox, 2007) and in the left inferior frontal cortex during a complex emotion recognition task (Hill et al., 2007), compared with FH- individuals.

However, even though these studies highlighted differences between FH+ and FH- individuals, several limitations make it hard to draw any definite conclusions regarding the neural correlates of social cognition in individuals at high risk for AUD. First, some FH+ samples included individuals with substance use and other psychiatric disorders. This is problematic, as the inclusion of FH+ individuals who have already developed AUD makes it impossible to disentangle the neural effects of prior vulnerability and those of severe alcohol consumption (Heitzeg, Nigg, Yau, Zubieta, & Zucker, 2008). Second, FH studies were mostly conducted with children and adolescents, whose brain maturation is still incomplete (Cservenka et al., 2014; Hulvershorn et al., 2013). However, individuals commonly develop AUD in adulthood, mostly between 20 and 40 years of age (Babor et al., 1992; Kapoor et al., 2016). Given the continuous nature of developmental trajectories, the existence of neural differences in FH+ children or adolescents may not be representative of the neural vulnerability at the age when AUD is typically triggered (Quach et al., 2020). Last, prior studies have always used emotional facial expressions to investigate social cognition processes in FH+ individuals despite the fact that social cognition is a multifaceted construct which is best evaluated through diverse experimental material (Cassel, McDonald, Kelly, & Togher, 2019). Hence, limiting FH studies to the decoding of emotional facial expressions hinders a more concise characterization of social cognition processes in FH+ individuals (Etchepare & Prouteau, 2018). If FH+ individuals display specificities during tasks which require mental state attribution beyond the mere decoding of socio-perceptual cues (i.e., mental state reasoning) remains an unanswered question to date (Thoma, Winter, Juckel, & Roser, 2013).

The aim of the present study was to address these shortcomings by investigating theory of mind abilities and their neural underpinnings (i.e., mental state reasoning) in FH+ individuals who were unaffected first-degree relatives (i.e., healthy adults without any substance use or major psychiatric disorder). Furthermore, we decided to focus on the distinction between cognitive and affective ToM which showed specific patterns of impairment in AUD patients and which, to our knowledge, has not yet been investigated among FH+ individuals.

Materials and methods

Participants

We enrolled 60 participants (30 FH+, 30 FH-) in this study. FH+ individuals were unaffected adults who had at least one first-degree family member (father or sibling) with current or past AUD according to DSM-5 criteria (American Psychiatric Association, 2013). Having a mother with current or past AUD was an exclusion criterion, to avoid the potential impact of alcohol consumption during pregnancy on neurocognitive functioning. The FH- group was composed of individuals who had no first-degree relative with current or past AUD or substance use disorder (excluding nicotine).

The FH+ and FH- groups were matched on age, sex, and education level, and did not differ on alcohol and nicotine consumption (Table 1). All participants were aged 18-60 years, native French speakers, and right-handed. Exclusion criteria were the presence of any substance use disorder (except nicotine dependence), behavioral addiction, or major neurological or psychiatric disorder with the potential to interfere with brain functioning. Participants had no contraindication for magnetic resonance imaging (MRI). Exclusion criteria were verified by a trained investigator through a face-to-face interview. All 60 participants met inclusion criteria and completed the entire study.

This study was conducted in accordance with the Declaration of Helsinki, approved by an institutional review board (ID-RCB: 2020-A00784-35) and preregistered on ClinicalTrials.gov (NCT04647422) as part of a larger research project. All participants gave their prior written informed consent and received €70 on completion of the study.

Materials and Procedure

Participants underwent two sessions. During the first session, a trained investigator conducted an extensive interview to collect sociodemographic and psychopathological variables (see below). Participants' intellectual abilities were assessed with the French version (Mackinnon & Mulligan, 2005) of the National Adult Reading Test, and their handedness with the Edinburgh Handedness Inventory (Oldfield, 1971). In the second session, participants underwent a task-based functional MRI (fMRI) scan. Before each session, breathalyzers were used to ensure the absence of any alcohol consumption prior to testing.

Psychopathology, alcohol, and nicotine use

The Mini-International Neuropsychiatric Interview for DSM-IV was used to assess the presence of common psychiatric disorders, including alcohol misuse and dependence (Sheehan et al., 1998). The Alcohol Use Disorder Identification Test (AUDIT; Gache et al., 2005) was administered to screen for any problematic alcohol consumption, while the Fagerström test (Heatherton, Kozlowski, Frecker, & Fagerström, 1991) was used to assess nicotine dependence. The severity of depressive symptoms was assessed with the shortened 13-item Beck Depression Inventory (BDI; Collet & Cottraux, 1986), and anxiety with the State-Trait Anxiety Inventory (STAI; Spielberger, Goruch, Lushene, Vagg, & Jacobs, 1983). The Childhood Trauma Questionnaire (CTQ; Paquette, Laporte, Bigras, & Zoccolillo, 2004) was used to evaluate the presence of five types of childhood trauma: sexual abuse, physical abuse, emotional abuse, physical neglect, and emotional neglect. The 20-item Toronto Alexithymia Scale (TAS-20; Bagby, Taylor, & Parker, 1994) was administered to evaluate

alexithymic traits. The TAS-20 yields a total score and three subscores: difficulties identifying feelings (DIF), difficulties describing feelings (DDF), and external-oriented thinking (EOT).

Family history density measure of AUD

FH of alcohol and other substance use was assessed through the Family Informant Schedule and Criteria (FISC) semi-structured interview (Mannuzza, Fyer, Endicott, & Klein, 1985), designed to assess the presence of AUD and substance use disorder in biological relatives (parents, full siblings, half-siblings, descendants). This information was used to calculate family history density (FHD) scores (see Pandey et al., 2020, for the detailed equation). FHD scores add additional information to any dichotomous FH approach comparing FH+ and FH- individuals by accounting for the number of family members with AUD. FHD is considered an indicator of premorbid AUD vulnerability, and descendants do not increase the risk for AUD from a temporal perspective, thus only non-descendant first-degree relatives (father, full siblings) were included in the equation. It should be noted that data on second-degree relatives (grandparents, aunts/uncles) is not collected with the FISC and was, therefore, not included in the equation.

fMRI task

A previously validated fMRI paradigm was used to assess ToM abilities (Sebastian et al., 2012; Vucurovic et al., 2022). Participants were presented with 30 short cartoon stories, each composed of three images. Of these cartoon stories, 10 assessed affective ToM (attribution of emotions to others), 10 assessed cognitive ToM (attribution of intentions to others), and 10 were stories of physical causality (PC) that did not require any mental state attribution (baseline). Each ToM story portrayed two protagonists and required participants to infer how they would feel or react in a social situation. After each story, two response images were displayed, and participants had to select the correct ending for the story by button-press. This task has been extensively described elsewhere (Sebastian et al., 2012).

fMRI data acquisition

The task was displayed using E-Prime 2.0 software (Psychology Software Tools Inc., Sharpsburg, PA, USA), and trials were arranged in a block design. Imaging was performed on a 3T Siemens Skyra® (Siemens Healthcare, Erlangen, Germany) scanner with a 20-channel head coil. Anatomical whole-brain T1-weighted images, parallel to the AC-PC line with a tilt of -25° , were collected for each participant. These were acquired using a gradient-echo pulse sequence with the following parameters: repetition time (TR) = 2800 ms, echo time (TE) = 6 ms, flip angle = 27° , 36 axial slices, slice thickness = 4 mm, 20% gap, matrix = 256 x 256, field of view (FOV) = 250 mm, reconstruction voxel size = 1 x 1 x 4 mm³. Whole-brain fMRI data were obtained through simultaneous multi-slice echoplanar imaging (SMS-EPI), allowing to achieve shorter TRs. Functional images were acquired with an interleaved-slice 2D-T2-weighted SMS-EPI sequence measuring changes in blood-oxygen-level-dependent (BOLD) contrast: TR = 1050 ms, TE = 30 ms, SMS acceleration factor = 2, flip angle = 62° , 36 axial slices, slice thickness = 4 mm, no gap, matrix = 80 x 80, FOV = 240 mm, voxel dimensions = 3 x 3 x 4 mm³. Images were acquired in the same axial plane as the T1-weighted anatomical images. A total of 706 volumes were acquired during a single 12-minute run.

fMRI data analysis

Imaging data were analyzed using Statistical Parametric Mapping Version 12 (SPM12; www.fil.ion.ucl.ac.uk/spm) implemented in MATLAB 2019 (The MathWorks, Inc., Natick, MA, USA). The six initial functional volumes were discarded for T1 stabilization. Preprocessing of imaging data included spatial realignment, slice-time correction, coregistration, segmentation and normalization to the standard anatomical space of the Montreal Neurological Institute (MNI). Functional scans were then spatially smoothed with an isotropic 3D Gaussian kernel of 10 mm FWHM.

Regressors of interest included in the first-level model were the onsets of the cartoon stories for the three conditions: cognitive ToM, affective ToM, and PC (baseline). Visual fixations and instructions were modeled as regressors of no interest. The six realignment parameters were included in the model to account for any variance due to head movement. Data were high-pass filtered at 128 Hz to remove low-frequency drifts.

At the first level, two contrasts of interest tested for significant ToM activation compared with baseline for each participant: Cognitive ToM > PC and Affective ToM > PC. These contrasts were then taken up to the second level and entered in one-sample *t* tests testing for brain activations during cognitive and affective ToM processing in the entire sample (FH+ and FH- groups combined) to assess the general effect of condition in the cartoon task. These first-level contrasts were then entered in separate two-sample *t* tests to directly compare the FH+ and FH- groups. The two-sample *t* tests were first run without covariables, then depressive symptoms (BDI total score), trait anxiety (STAI-B total score) and childhood trauma (CTQ total score) were included as covariables in the second-level models. In all analyses, clusters reaching a familywise error (FWE) threshold of $p < .05$ were retained and labeled using the third version of the Automated Anatomical Labeling atlas (AAL3; Rolls, Huang, Lin, Feng, & Joliot, 2020).

First eigenvariates were extracted at cluster-level for second-level clusters reaching significance in the two-sample *t* tests including covariates. Spearman correlation coefficients were used to test the association between these first eigenvariates, sociodemographic and clinical variables, FHD scores, alexithymia and behavioral performances on the cartoon task (total % of correct responses for cognitive and affective ToM stories) in the FH+ group. Bonferroni corrections were applied to *p* values.

Statistical analyses of behavioral data were conducted using the Statistical Package for the Social Sciences (SPSS 24; IBM Corp., Armonk, NY, USA). Results were considered significant at $p < .05$.

Results

Group Comparison

The demographic and clinical characteristics of the FH+ and FH- groups are displayed in Table 1. They were comparable on age, sex ratio, education level, IQ, and alcohol and nicotine consumption. However, the FH+ group had higher levels of anxiety and depressive symptoms (albeit below the standard cut-off), as well as more frequent childhood trauma compared with the FH- group. According to the CTQ interpretation guidelines, sexual abuse, emotional abuse, physical neglect, and emotional neglect were in the low/moderate range for the FH+ group, and the none/minimal range for the FH- group. Physical abuse was in the none/minimal range for both groups. Moreover, the FH+ group displayed higher alexithymic traits and experienced more difficulties in identifying their own feelings than the FH- group.

Behavioral data

Performances on the cartoon task are reported in Table 2. FH+ and FH- groups did not differ on the rate of correct responses for cognitive ToM ($p = .243$), but significantly differed on affective ToM ($p = .040$), with lower performances in the FH+ group. No group difference was observed for PC stories ($p = .707$) and response times for cognitive ToM, affective ToM, and PC did not differ between groups (all $ps > .170$).

fMRI data

Effect of Condition

Regions reaching cluster-level significance in the one-sample t tests at $p < .05$ (FWE-corrected) testing for brain activations associated with cognitive and affective ToM in the

entire sample are included as supplementary material (Supplement S1). Both, cognitive and affective ToM were associated with brain activations in the precuneus, middle and superior temporal cortices, temporal poles, and inferior frontal gyrus. However, cognitive ToM processing also elicited neurofunctional changes in the gyrus supramarginalis and the parahippocampal gyrus which were not observed for affective ToM. Conversely, affective ToM elicited more neurofunctional changes in the anterior and midcingulate cortex, and the ventromedial prefrontal cortex, contrary to cognitive ToM.

Effect of Group

Regions reaching cluster-level significance in the two-sample t tests at $p < .05$ (FWE-corrected) are displayed in Table 3. For the contrast Cognitive ToM > PC, no significant clusters were found, indicating no differences in brain activation in the FH+ and FH- groups during cognitive ToM processing compared with baseline. For the contrast Affective ToM > PC, the FH+ group showed differences in brain activation in two significant clusters compared with the FH- group (Figure 1 upper half). The first cluster (C1) comprised parts of the left middle frontal cortex and precentral gyrus and the second cluster (C2) parts of the left insula and inferior frontal cortex (pars triangularis, opercularis, and orbitalis). Whereas these regions were deactivated by the FH- group during affective ToM processing compared with baseline, they were more strongly activated by the FH+ group (Figure 1 lower half). The reverse contrast testing for decreased brain activation in the FH+ compared to the FH- group during affective ToM processing compared to baseline did not yield any significant results.

When conducting the same analyses with depressive symptoms, anxiety, and childhood trauma as covariates, higher brain activations for the contrast Affective ToM > PC in the FH+ group compared to the FH- group only survived in C2, that is in the cluster comprising parts of the left insula and inferior frontal cortex (Figure 2).

The SPM T maps of these analyses have been publicly uploaded to Neurovault (Gorgolewski et al., 2015) and can be accessed via the following link: <https://neurovault.org/collections/IZLUJWED/>.

Correlational analyses

In the FH+ group, the first-eigenvariate at cluster-level extracted for the C2 cluster controlling for covariates (BDI, STAI, CTQ) was neither significantly correlated with age ($p = .877$), education level ($p = .693$), IQ ($p = .449$), AUDIT ($p = .471$) nor with FHD scores ($p = .211$) (Supplement S2). Moreover, task-performances on the cartoon task (% of correct responses for the cognitive and affective ToM stories) and alexithymia were unrelated to brain activity in the FH+ group (all $ps > .182$).

Discussion

The aim of the present study was to assess the neural correlates of cognitive and affective ToM in first-degree relatives of AUD patients. Even though differences in social cognition may precede or be concomitant with the onset of AUD, no prior study had examined differences in ToM functioning as a potential marker of vulnerability for AUD.

Results indicated that FH+ individuals differed from FH- individuals, at both behavioral and neural levels. At the behavioral level, FH+ individuals had poorer response accuracy in a validated fMRI ToM task, and these difficulties were particularly pronounced for affective ToM given that FH+ and FH- individuals did not differ on the cognitive ToM stories. Importantly, the differences we observed in response accuracy cannot be attributed to more general difficulties during task completion, given that the two groups had equivalent performances in the baseline condition (physical causality).

In addition, FH+ individuals had higher brain activation than FH- individuals (who showed deactivations) during affective ToM processing compared to baseline in the left

precentral gyrus, middle frontal cortex, insula, and inferior frontal cortex, notably in the pars triangularis, opercularis and orbitalis. Importantly, higher brain activation in the left insula and inferior frontal cortex were still observed during affective ToM processing after controlling for depressive symptoms, anxiety, and childhood trauma. Hence, these variables were not able to entirely explain the differential brain activation observed in FH+ individuals and the left insula and inferior frontal cortex seem to be regions which show a specific association with a FH of AUD. Conversely, no differences in neural activation between the FH+ and FH- groups emerged for cognitive ToM processing compared to baseline.

Hence, the behavioral and neural findings of this study are consistent with prior research on AUD highlighting more severe affective versus cognitive ToM impairments in AUD, thereby suggesting that affective ToM plays a preponderant role and that emotional difficulties are core features of this disorder (Le Berre, 2019; Maurage et al., 2016). This similar pattern of dissociation between affective and cognitive ToM abilities in FH+ individuals and AUD patients further strengthens the idea that some ToM specificities may already be present prior to AUD development and may be underpinned by genetic and/or shared environmental factors.

Our behavioral and neural findings indicate that the efficiency and processing mechanisms of affective ToM differ in FH+ individuals. Frontal and insular brain regions have been consistently associated with ToM networks in the literature (Henry et al., 2021; Mar, 2011; Schlaffke et al., 2015). The insula allows for the identification of interoceptive cues and is a key region for empathic and mentalizing abilities (Carr, Iacoboni, Dubeau, Mazziotta, & Lenzi, 2003; Wang et al., 2019). It has been suggested that the insula may be crucial for affective ToM and contribute to the understanding of emotions through a mechanism of affective resonance implying the simulation of behavioral and physiological reactions of others by oneself (Corradi-Dell'Acqua et al., 2020). The mechanisms associated

with this simulation of internal states may differ in FH+ participants and hamper insights into mental states. The presence of higher alexithymic traits in the FH+ group of our study lends further evidence to this hypothesis and indicated compromised abilities in FH+ individuals to identify their own feelings and internal states. Yet, the neural mechanisms underlying ToM processes and the specific role of the insula are still not clearly established in the general population and this hypothesis therefore needs further clarification (Zeng et al., 2020).

Importantly, prior research also revealed neurofunctional differences in the insula and the inferior frontal cortex in individuals at risk for AUD (DeVito et al., 2013) and has highlighted the relevance of an introspective socio-affective network comprising the orbitofrontal cortex, the insula and the cingulate cortex in AUD development (Hill & O'Brien, 2015). Higher activation in the left insula was found in AUD high-risk adolescents during the presentation of emotional words (Heitzeg et al., 2008). Furthermore, resting-state analyses revealed hyperconnectivity between striatal regions and the inferior frontal cortex, the precentral gyrus, and the insula in FH+ individuals (Ersche et al., 2020). Our results take these findings one step further, by showing that brain activation in these regions also differs during affective ToM processing in FH+ versus FH- individuals.

Furthermore, our study allowed to reduce the impact of possible confounding variables (sex, age, education level, alcohol and nicotine consumption, anxiety, depressive symptoms, childhood trauma) through a strict matching procedure and the inclusion of covariates in the analyses. A FH of AUD is known to be associated with a higher risk for AUD through shared genetic and environmental factors. Psychopathological variables, such as anxiety, depression, and childhood trauma have been evoked as factors which might be driving this increased risk (Cheng et al., 2020; Kisely, Mills, Strathearn, & Najman, 2020). Our results indeed indicated more frequent depressive symptoms, anxiety, and childhood trauma in FH+ individuals but also showed that these variables were only partly related to the differences in brain activation

between our groups given that a large cluster remained significant after controlling for these variables. A FH of AUD may increase the risk for neurofunctional differences through a combination of multiple genetic and environmental factors.

It would be interesting for future studies to unravel the impact and weight of different genetic and environmental factors regarding ToM difficulties in FH+ individuals and to study their association with AUD development. Studies could for instance explore the genetic variations which contribute to ToM difficulties in this population and should address if the exposure to an AUD first-degree relative during critical developmental periods is particularly harmful for ToM abilities. Variables such as the type of family member affected by AUD (father, sibling and also mother), a shared living environment and relational closeness may differentially impact ToM functioning in FH+ individuals. In the present sample, FHD scores were unrelated to brain activity in the FH+ group in the follow-up correlational analyses. Differences in brain activation in FH+ participants might hence be present irrespective of the number of first-degree relatives with AUD within a family. However, this finding needs further replication and future studies should use extensive FHD calculation methods considering the presence of AUD in all first and second-degree family members to further explore the relationship between FHD and ToM processing.

Another interesting result was the presence of contrasting brain activation patterns in the FH+ and FH- groups. Whereas the FH+ group displayed higher brain activation in significant regions during affective ToM processing compared with baseline, deactivation of these significant regions was found in the FH- group. There are two possible explanations: first, FH+ individuals may have to recruit additional regions to compensate at least partially for ToM difficulties, in which case higher brain activation could be considered a resiliency factor against AUD (Hulvershorn et al., 2013). Second, the activation of these regions may reflect less refined ToM networks in FH+ individuals, in which case the recruitment of

additional regions could lead to increased vulnerability for AUD (Ersche et al., 2020). Indeed, genetic studies provide heritability estimates of approximately 50% for AUD (Verhulst, Neale, & Kendler, 2015). Given that FH+ participants share half of their genes with their first-degree family members presenting an AUD, chances are high that they partly inherited existing vulnerability markers. Still, the FH+ participants of this study were healthy adults without AUD or any major psychiatric condition. It is therefore likely that they also possess resiliency factors protecting against AUD development prior to study inclusion. Disentangling vulnerability and resiliency factors in neuroscience studies is not straightforward.

In our study, several arguments seem in favor of the vulnerability hypothesis and need to be highlighted. First, the presence of higher alexithymic traits and lower affective theory of mind performances at the behavioral level seem to reflect vulnerability markers. Second, the FH+ individuals had higher brain activation, irrespective of task performance, as shown by the follow-up correlational analyses. Third, this reversed pattern of activation and deactivation was already observed in the princeps study of this fMRI ToM task: whilst healthy adolescents more strongly activated parts of the inferior frontal cortex during ToM processing, similar to the FH+ individuals in our study, these regions were deactivated by healthy adults (Sebastian et al., 2012). The authors interpreted this higher brain activation during adolescence as the reflection of immature ToM networks. We might therefore consider that the neural maturation of ToM networks is compromised in FH+ individuals (Spadoni, Simmons, Yang, & Tapert, 2013). However, these interpretations must be treated with caution and further research is warranted to disentangle vulnerability and resiliency factors for AUD in FH+ participants.

In this context, several limitations should be acknowledged. First, our study was cross-sectional and therefore did not allow us to describe potential changes in ToM processing related to AUD vulnerability. Future studies should use a longitudinal design to determine whether differential neural activations in FH+ participants represent vulnerability or resiliency

factors for AUD. Second, our study did not include FH+ individuals whose mother presented AUD to prevent confounding effects of in-utero alcohol consumption. Therefore, future studies are warranted to address the potential genetic and/or environmental contribution of a female parent with AUD to ToM processing and AUD development. In this context, it must be noted that FHD scores vary depending on the type of family members included in the equation and this may have influenced the results of the correlational analyses presented in this study. Third, the sample size of this study may have been insufficient to capture small effect sizes. Future studies should be conducted to replicate these findings with larger sample sizes.

In conclusion, this study is the first to highlight neural and behavioral differences during affective ToM processing in healthy FH+ adults. Given that ToM abilities are crucial for social bonding, ToM difficulties most likely come at a cost, and may impede the establishment of fruitful social relationships (Byom & Mutlu, 2013). It is therefore essential to gain a full picture of social cognition abilities in individuals at high risk for AUD, in order to shape prevention programs and ensure that interpersonal problems do not serve as a trigger for AUD (Le Berre, Fama, & Sullivan, 2017; Lewis et al., 2019). Since AUD is characterized by a wide range of social cognition impairments, investigations of other social cognition processes (e.g., empathy, emotion regulation) in FH+ individuals would be insightful.

Supplementary material. The supplementary material for this article can be found at [please insert final doi here].

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Figure legends

Figure 1. Results from the two-sample t tests without covariates for the contrast Affective ToM > PC. Left: The brain activation in the FH+ and FH- groups differed in the left precentral gyrus and middle frontal cortex. Right: The brain activation in the FH+ and FH- groups differed in the left insula and inferior frontal cortex (pars opercularis, orbitalis and triangularis). The FH+ group had higher activations whilst the FH- group had lower activations during affective ToM processing compared to baseline. The statistics associated with these two-sample t tests are presented in the upper half of Table 3. p FWE-corr < .05 cluster-forming threshold for family wise error. p < .001 voxel-wise threshold; $k = 395$. Error bars indicate standard errors of the mean.

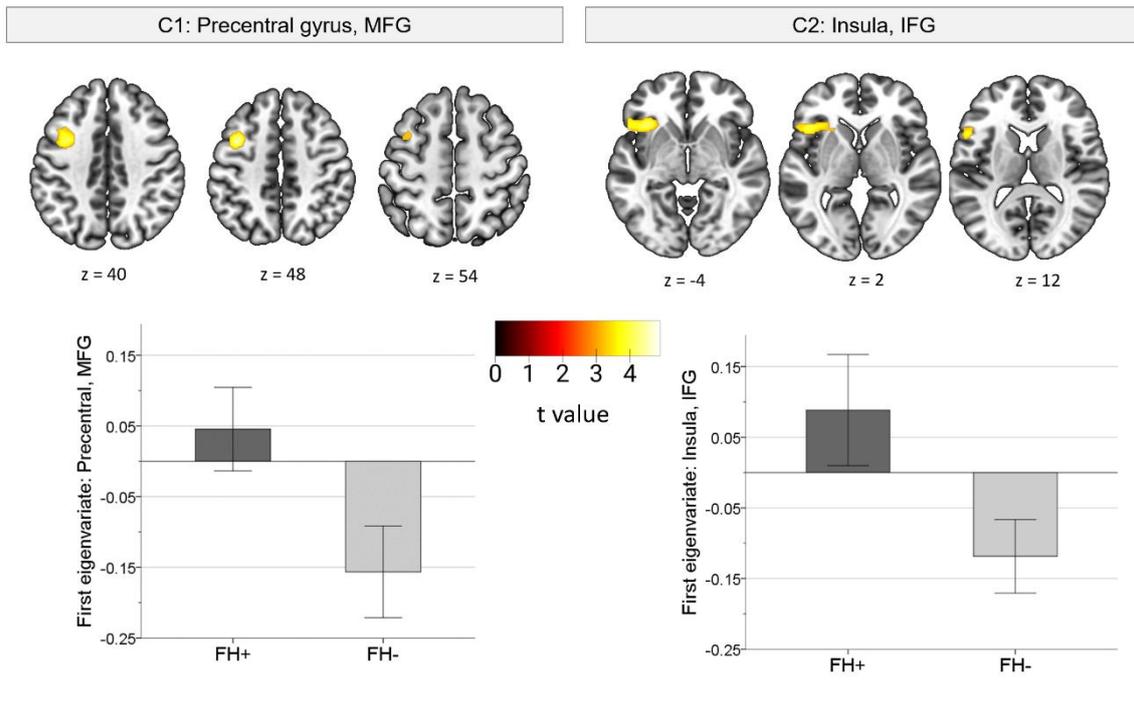


Figure 2. Results from the two-sample t tests showing intergroup differences for the contrast Affective ToM > PC, controlling for depressive symptoms, anxiety, and childhood trauma. The FH+ group had higher activations during affective ToM processing compared to baseline in the left insula and inferior frontal cortex (pars orbitalis and triangularis). The statistics associated with these two-sample t tests are presented in the lower half of Table 3. p FWE-corr < .05 cluster-forming threshold for family wise error. p < .001 voxel-wise threshold; $k = 470$.

C2: Insula, IFG

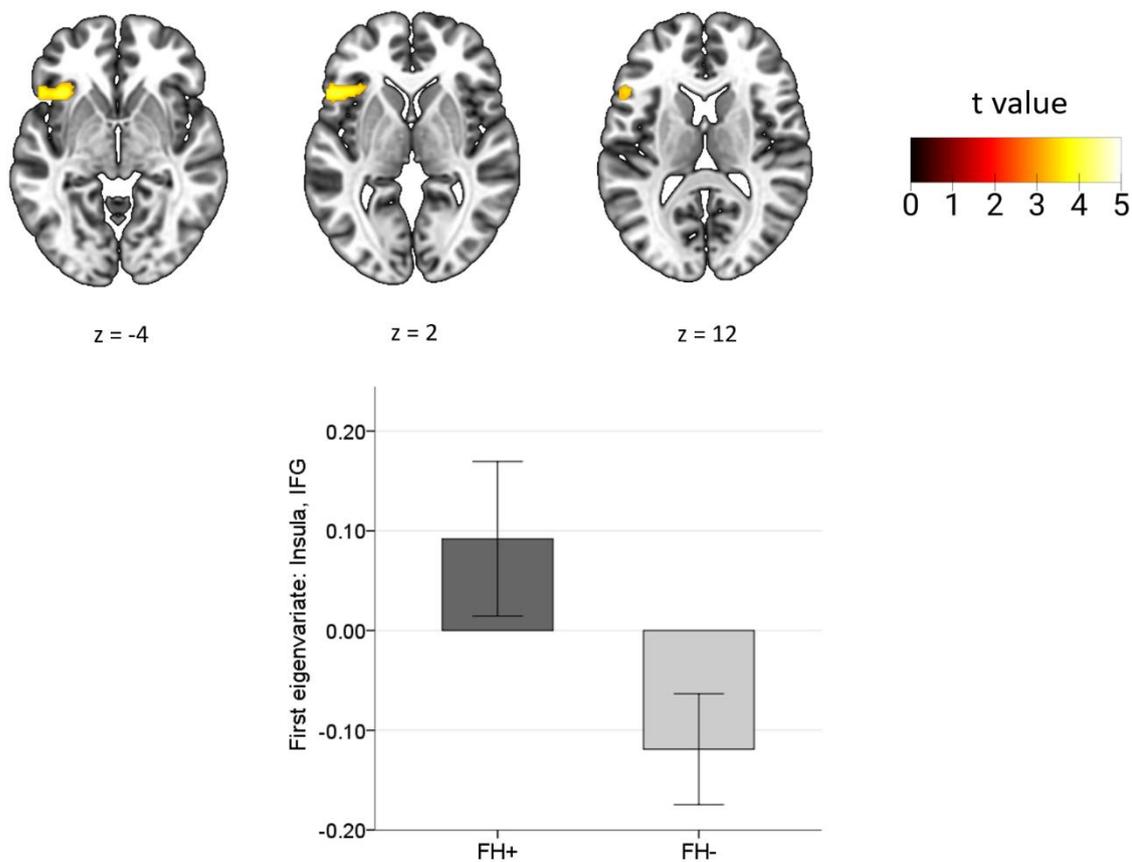


Table 1. Demographic and clinical characteristics of FH+ and FH- participants

	FH+ group (n = 30)	FH- group (n = 30)	p value
<i>Demographics</i>			
Age (years)	39.10 (10.35)	37.73 (10.57)	.615
Sex-ratio (F/M)	20/10	21/9	.781
Education level (years)	14.17 (2.31)	14.07 (1.98)	.989

NART total IQ	107.51 (6.94)	106.90 (6.43)	.725
<i>Alcohol related variables and tobacco use</i>			
AUDIT total score	3.27 (2.21)	2.97 (2.24)	.362
Alcohol units per week	3.00 (3.45)	2.09 (2.20)	.115
Current smokers (%)	16.67	20.00	.739
Pack years ^a	7.40 (5.31)	5.70 (6.29)	.657
FTND score ^a	3.40 (0.89)	2.00 (2.68)	.397
<i>Family drinking history</i>			
Number of AUD 1 st degree relatives	1.47 (0.94)	/	
Fathers with AUD (%)	83.33	/	
Siblings with AUD (%)	43.33	/	
FHD score	0.37 (0.16)	0.00 (0.00)	< .001
<i>Mood and anxiety</i>			
BDI-13	3.73 (2.90)	1.57 (2.11)	.001
STAI-A	29.07 (8.63)	24.33 (7.88)	.003
STAI-B	38.93 (9.90)	32.87 (7.64)	.011
<i>Childhood trauma</i>			
CTQ total score	45.23 (17.06)	31.53 (6.86)	< .001
CTQ Sexual abuse	6.23 (3.78)	5.00 (0.00)	.005
CTQ Physical abuse	7.40 (4.32)	5.63 (1.33)	.216
CTQ Emotional abuse	10.17 (5.36)	6.30 (1.95)	.005
CTQ Physical neglect	8.10 (3.16)	5.70 (0.95)	.001
CTQ Emotional neglect	13.33 (5.48)	8.90 (3.99)	.001
<i>Alexithymia</i>			
TAS-20 total score	42.33 (13.22)	36.27 (7.45)	.034
TAS-20 DIF	13.30 (5.84)	9.70 (2.96)	.014
TAS-20 DDF	12.83 (5.42)	10.37 (4.67)	.077
TAS-20 EOT	16.20 (4.34)	16.20 (2.87)	.999

FH+, Positive Family History; FH-, Negative Family History; NART, National Adult Reading Test; AUDIT, Alcohol Use Disorder Identification Test; FTND, Fagerström Test for Nicotine Dependence; FHD, Family History Density; BDI-13, 13-item Beck Depression Inventory; STAI, State Trait Anxiety Inventory; CTQ, Childhood Trauma Questionnaire; TAS, 20-item Toronto Alexithymia Scale; DIF, Difficulty Identifying Feelings; DDF = Difficulty Describing Feelings; EOT, External-Oriented Thinking.

Notes: Data are means (standard-deviation), unless otherwise specified. Group differences were examined with *t* tests. Mann-Whitney *U* tests were used when the normality assumption was violated. Significant *p* values are highlighted in bold.

^a Means were calculated for smokers only (*n*_{FH+} = 5, *n*_{FH-} = 6). Data of one participant were missing for pack years (*n*_{FH+} = 5, *n*_{FH-} = 5).

Table 2. Behavioral data for the FH+ and FH- groups in the cartoon task: mean (standard-deviation)

	FH+ group (n = 30)	FH- group (n = 30)	<i>p</i> value	Cohen's <i>d</i>
<i>Response Accuracy (%)</i>				
ToM total	93.00 (5.19)	96.50 (3.75)	.005	-0.79
Cognitive ToM	94.67 (6.81)	96.67 (5.47)	.243	-0.30
Affective ToM	91.33 (10.08)	96.33 (5.56)	.040	-0.55
Physical causality	88.00 (14.48)	91.33 (8.19)	.707	-0.01
<i>Response Times (ms)</i>				
ToM total	2 659.25 (475.00)	2 827.69 (464.39)	.170	-0.37
Cognitive ToM	2 620.34 (534.35)	2 802.62 (489.05)	.173	-0.36
Affective ToM	2 698.16 (539.04)	2 852.76 (522.23)	.264	-0.30
Physical causality	2 806.41 (694.03)	3 027.90 (675.98)	.216	0.33

FH+, Positive Family History; FH-, Negative Family History; ToM, Theory of Mind.

Notes: Group differences were examined with *t* tests. Mann-Whitney *U* tests were used when the normality assumption was violated. Significant *p* values are highlighted in bold.

Table 3. Higher whole-brain activations for the contrast Affective ToM > PC when comparing the FH+ and FH- groups (two-sample *t* tests). Analyses were run without covariates and controlling for depressive symptoms, anxiety, and childhood trauma.

Location						MNI coordinates		
Areas	Hemisphere	Brodmann area	Cluster size	$p_{\text{FWE-corr}}$	<i>t</i> value	x	y	z
A. FH+ > FH without covariates								
<i>Cluster C1</i>								
Precentral gyrus	L	6	395	.041	4.95	-38	4	44
MFG	L	9,44						
<i>Cluster C2</i>								
Insula	L	47	692	.005	4.25	-34	22	-2
IFG triangularis	L	45						
IFG orbitalis	L	47,48						
IFG opercularis	L	45						
B. FH+ > FH- with covariates								
<i>Cluster C2</i>								
IFG triangularis	L	45	470	.025	4.17	-40	22	-2
Insula	L	47						
IFG orbitalis	L	47,48						

FH+, Positive Family History; FH-, Negative Family History; ToM, Theory of Mind; PC, Physical Causality; MFG, Middle Frontal Gyrus; IFG, Inferior Frontal Gyrus; L, Left; R, Right.
 $p_{\text{FWE-corr}}$ = cluster-forming threshold for family wise error. $p < .001$ voxel-wise threshold.

Other Supplementary Material

Supplement S1. Whole-brain activations during cognitive and affective ToM processing in the total sample, controlling depressive symptoms, anxiety, and childhood trauma (one-sample *t* tests)

Location						MNI coordinates		
Areas	Hemisphere	Brodmann area	Cluster size	$p_{\text{FWE-corr}}$	t value	Cluster peak		
						x	y	z
<i>Cognitive ToM > PC</i>								
Precuneus, posterior cingulate	L	5, 23	15 213	< .001	13.55	-6	-50	46
Parahippocampal gyrus	L	30, 37	1 468	< .001	10.79	-26	-44	-8
MTG, Temporal poles	R	21, 22	1 224	< .001	10.75	54	0	-22
Cerebellum	L	-	914	.001	6.50	-6	-52	-44
<i>Cognitive ToM < PC</i>								
Supramarginal gyrus	R	2, 40	2 940	< .001	9.62	54	-30	46
MFG	R	45	1 927	< .001	9.16	46	42	6
IFG triangularis	L	45, 47	1 894	< .001	8.39	-44	38	8
IPG	L	40	1 453	< .001	8.15	-58	-34	46
IFG opercularis	R	44, 48	1 029	.001	7.97	48	8	20
IFG opercularis	L	44, 48	1 070	< .001	6.88	-46	10	14
SFG, anterior cingulate	R	8, 32	1 177	< .001	5.94	6	26	42
Lingual	L	17	2 399	< .001	5.78	0	-82	2

Supplement S1 (continued). Whole-brain activations during cognitive and affective ToM processing in the total sample, controlling depressive symptoms, anxiety, and childhood trauma (one-sample *t* tests)

Location						MNI coordinates		
						Cluster peak		
Areas	Hemisphere	Brodmann area	Cluster size	$p_{\text{FWE-corr}}$	t value	x	y	z
<i>Affective ToM > PC</i>								
Precuneus, posterior cingulate	R	23, 30	10 139	< .001	13.25	4	-52	36
STG, MTG	R	21, 22	5 787	< .001	10.59	54	-48	16
Medial SFG, anterior cingulate	R	10, 32	3 554	< .001	9.43	10	56	16
<i>Affective ToM < PC</i>								
Calcarine	R	17, 18	16 546	< .001	14.79	18	-92	0
IFG opercularis	L	44, 48	2 741	< .001	9.59	-44	6	26
SFG	R	8, 9	958	.002	8.46	30	16	56
IFG opercularis	R	44, 48	897	.003	7.90	48	8	20
MFG, Premotor	L	6, 8	738	.007	7.31	-26	12	56
MFG	R	45, 46	1 392	< .001	7.28	46	40	10
Medial SFG, anterior cingulate	R	32	536	.022	7.21	6	30	40

ToM, Theory of Mind; PC, Physical Causality; MTG, Middle Temporal Gyrus; MFG, Middle Frontal Gyrus; IFG, Inferior Frontal Gyrus; IPG, Inferior Parietal Gyrus; SFG, Superior Frontal Gyrus; L = Left; R = Right.

$p_{\text{FWE-corr}}$ = cluster-forming threshold for family wise error. $p < .001$ voxel-wise threshold.

Supplement S2. Spearman correlation coefficients between task-based first eigenvariates at cluster-level, family history density, sociodemographic and clinical variables, and task performance in the FH+ group.

	FHD	Age	Education level	NART total IQ	AUDIT total score	TAS-20 total score	Cognitive ToM (%)	Affective ToM (%)
First eigenvariate for the C2 cluster with covariates	.235	.029	-.075	.144	-.137	.032	.167	-.250

FH+, Positive Family History; FHD, Family History Density of alcohol use disorders; NART, National Adult Reading Test; AUDIT, Alcohol Use Disorder Identification Test; TAS-20, 20-item Toronto Alexithymia Scale; ToM, Theory of Mind; C2, Cluster 2 comprising parts of the left insula and the inferior frontal cortex.

Notes: First eigenvariates were extracted for the cluster comprising the left insula and inferior frontal cortex remained significant after controlling for depressive symptoms, anxiety, and childhood trauma in the two-sample *t* tests. Given that depressive symptoms, anxiety, and childhood trauma were included as covariates at the second level, they were no longer significantly associated with the first eigenvariates and were hence not included in the correlation matrices. Correlations with FHD scores were not computed for the FH- group given that these participants all had FHD scores equal to zero. Significant correlations at $p < 0.05$ after Bonferroni correction are highlighted in bold.