



**HAL**  
open science

## Exploratory case study of monozygotic twins with 22q11.2DS provides further clues to circumscribe neurocognitive markers of psychotic symptoms

Emilie Favre, Arnaud Leleu, Elodie Peyroux, Jean Yves Baudouin, Nicolas Franck, Caroline Demily

### ► To cite this version:

Emilie Favre, Arnaud Leleu, Elodie Peyroux, Jean Yves Baudouin, Nicolas Franck, et al.. Exploratory case study of monozygotic twins with 22q11.2DS provides further clues to circumscribe neurocognitive markers of psychotic symptoms. *Neuroimage-Clinical*, 2019, 24, pp.101987. 10.1016/j.nicl.2019.101987 . hal-02275563

**HAL Id: hal-02275563**

**<https://hal.science/hal-02275563>**

Submitted on 25 May 2020

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial - NoDerivatives 4.0 International License



## Exploratory case study of monozygotic twins with 22q11.2DS provides further clues to circumscribe neurocognitive markers of psychotic symptoms

Emilie Favre<sup>a,b,\*</sup>, Arnaud Leleu<sup>c</sup>, Elodie Peyroux<sup>a,b,e</sup>, Jean-Yves Baudouin<sup>c,d</sup>, Nicolas Franck<sup>b,e</sup>, Caroline Demily<sup>a,b</sup>

<sup>a</sup> GéoPsy, Centre de Référence Maladies Rares à Expression Psychiatrique, Centre Hospitalier Le Vinatier, 95 bd Pinel BP300.91, F-69 678 BRON Cedex, France

<sup>b</sup> Equipe EDR-Psy, Institut de Sciences Cognitives Marc Jeannerod, CNRS-UMR5229 & Université Lyon 1 Claude Bernard, 67 bd Pinel, F-69 500 BRON, France

<sup>c</sup> Equipe Éthologie Développementale et Psychologie Cognitive, Centre des Sciences du Goût et de l'Alimentation, AgroSup Dijon, UMR 6265 CNRS, UMR 1324 INRA, Université Bourgogne Franche-Comté, 9 bd Jeanne d'Arc, F-21 000 Dijon, France

<sup>d</sup> Laboratoire Développement, Individu, Processus, Handicap, Education (DIPHE), Département Psychologie du Développement, de l'Éducation et des Vulnérabilités (PsyDEV), Institut de psychologie, Université Lumière Lyon 2, 5 av Pierre Mendès-France, F-69676 Bron, France

<sup>e</sup> Centre ressource pour la réhabilitation psychosociale et la médiation cognitive, Centre Hospitalier Le Vinatier, 5 rue Jean Sarrazin, F-69 008 Lyon, France

### ARTICLE INFO

#### Keywords:

22q11.2DS

Facial expression perception

Endophenotype

Psychotic symptoms

Frequency-tagging

Electroencephalography

### ABSTRACT

Variation in facial emotion processing abilities may contribute to variability in penetrance for psychotic symptoms in 22q11.2DS. However, the precise nature of the social cognitive dysfunction (i.e., facial expression perception vs. emotion recognition), the potential additional roles of genetic and environmental variabilities, and consequently the possibility of using this neurocognitive marker in clinical monitoring remain unclear. The present case study aimed at testing the hypothesis that when confounding factors are controlled, the presence of psychotic symptoms in 22q11.2DS is associated, at the individual level, with a neural marker of facial expression perception rather than explicit emotional face recognition. Two monozygotic twins with 22q11.2DS discordant for psychiatric manifestations performed (1) a classical facial emotion labelling task and (2) an implicit neural measurement of facial expression perception using a frequency-tagging approach in electroencephalography (EEG). Analysis of the periodic brain response elicited by a change of facial expression from neutrality indicated that the twin with psychotic symptoms did not detect emotion among neutral faces while the twin without the symptoms did. In contrast, both encountered difficulties labelling facial emotion. The results from this exploratory twin study support the idea that impaired facial expression perception rather than explicit recognition of the emotion expressed might be a neurocognitive endophenotype of psychotic symptoms that could be reliable at a clinical level. Although confirmatory studies should be required, it facilitates further discussion on the etiology of the clinical phenotype in 22q11.2DS.

### 1. Introduction

22q11.2 deletion syndrome (22q11.2DS) affects several organs including brain structure and function (Boot and Amelsvoort, 2012). It manifests as various neuropsychiatric symptoms such as cognitive dysfunction, autism spectrum disorder or attention deficit hyperactive disorder (Schneider et al., 2014). 22q11.2DS represents one of the largest known genetic risk factors for schizophrenia. Lifetime prevalence of schizophrenia is approximately 25% in 22q11.2DS compared

to approximately 1% in the general population (Owen and Doherty, 2016). Identifying stable neurocognitive markers that contribute to understand and predict the psychiatric phenotype in 22q11.2DS is thus of high relevance for early schizophrenia prevention.

Social cognition dysfunction, and more specifically emotional face perception, was proposed as a robust endophenotype of schizophrenia (Gur et al., 2006; Sabharwal et al., 2017). The underlying assumption is that misinterpretation of other's emotional state may participate in behaviors characterized by hostility, delusion, aggression, and social

**Abbreviations:** 22q11.2DS, 22q11.2 deletion syndrome; EEG, electroencephalography; PANSS, Positive And Negative Syndrome Scale; CHG-Array, complete genomic hybridization; FISH, fluorescent in situ hybridization; FEP measurement, Facial expression perception measurement

\* Corresponding author at: GéoPsy, Centre de Référence Maladies Rares à Expression Psychiatrique, Centre Hospitalier Le Vinatier, 95 bd Pinel BP300.91, F-69 678 BRON Cedex, France.

E-mail addresses: [emilie.favre@ch-le-vinatier.fr](mailto:emilie.favre@ch-le-vinatier.fr) (E. Favre), [arnaud.leleu@u-bourgogne.fr](mailto:arnaud.leleu@u-bourgogne.fr) (A. Leleu), [elodie.peyroux@ch-le-vinatier.fr](mailto:elodie.peyroux@ch-le-vinatier.fr) (E. Peyroux), [j.baudouin@univ-lyon2.fr](mailto:j.baudouin@univ-lyon2.fr) (J.-Y. Baudouin), [nicolas.franck@ch-le-vinatier.fr](mailto:nicolas.franck@ch-le-vinatier.fr) (N. Franck), [caroline.demily@ch-le-vinatier.fr](mailto:caroline.demily@ch-le-vinatier.fr) (C. Demily).

<https://doi.org/10.1016/j.nicl.2019.101987>

Received 14 December 2018; Received in revised form 16 July 2019; Accepted 16 August 2019

Available online 17 August 2019

2213-1582/ © 2019 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license

(<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

withdrawal. One key mechanism to understand others' mental state is the ability to perceive and recognize facial expressions. Actually, a deficit in facial emotion processing is widely observed in children and young adults with 22q11.2DS (Badoud et al., 2017; Campbell et al., 2015; Leleu et al., 2016; McCabe et al., 2016; Norkett et al., 2017). Surprisingly, only few studies reported that it might increase the risk of psychotic transition (Antshel et al., 2016; Badoud et al., 2017; Jalbrzikowski et al., 2012, 2014; Weinberger et al., 2016) while more extensive data incriminated deficits in complex social cognitive processes (i.e., theory of mind and perspective taking) or executive functions (Antshel et al., 2016; Jalbrzikowski et al., 2012, 2014; Schneider et al., 2014; Tang and Gur, 2017; Vorstman et al., 2015; Weinberger et al., 2016).

Hence, deeper investigations are needed to determine whether facial emotion processing could be a neurocognitive endophenotype of psychotic symptom in 22q11.2DS and rule out possible confounding explanations. The first issue concerns the specificity of emotional face perception measurement when using standard behavioural tasks. For instance, the widely used emotional face labelling tasks are unable to disentangle the contribution of automatic facial expression perception (i.e., visual processing of a change of facial expression) and explicit facial emotion recognition (i.e., emotion attribution to an expressive facial percept). Critically, behavioural measures can be contaminated by response-related unspecific processes such as decision-making or response inhibition (Azuma et al., 2015; Leleu et al., 2016). Second, classical group studies insufficiently control genetic or environmental stress variability that could mediate the incomplete penetrance for psychiatric phenotypes (Biswas and Furniss, 2016; Chung et al., 2015; Guipponi et al., 2017; Toyosima et al., 2011). It remains thus unclear whether neurocognitive markers identified in group studies can be used in clinical care, i.e., for individual participants.

To circumvent these limitations, the present study reports a case of monozygotic twins who are discordant for psychiatric symptoms. Twin studies are a valuable source of information on genotype-phenotype relationship. In the field of schizophrenia research, they recently raised several hypotheses on the etiology of psychotic symptoms, including post zygotic mutations (Castellani et al., 2017), somatic mutations (Nishioka et al., 2018), or inflammatory processes (Braun et al., 2017). In 22q11.2DS, although previous twin studies in childhood reported discordance for heart defect (Goodship et al., 1995; Halder et al., 2012), none has yet addressed psychiatric symptoms in adults. In the present study, twins with 22q11.2DS were submitted to a classical emotion recognition labelling task and a frequency-tagging approach in electroencephalography (EEG) to disentangle their ability to perceive a change of facial expression from the recognition of the emotion expressed. This EEG approach provides an implicit neural measurement of facial expression perception exempt from other unspecific processes and is adapted to single case designs with the significance of individual brain responses estimated in healthy participants in previous studies (Dzhelyova et al., 2017; Leleu et al., 2018; Liu-Shuang et al., 2014; Norcia et al., 2015; Poncet et al., 2019). The present study thus represents a privileged opportunity to highlight reliable endophenotypes of psychiatric symptoms at an individual level since the participants share most genetic and environmental confounding factors and the measurement specifically quantifies perceptual response to expressive faces without being influenced by decision and labelling-related processes.

## 2. Materials and methods

The study was carried out in accordance with the latest version of the Declaration of Helsinki. The experimental procedure was approved by the ethic committee CPP SUD-EST II (ANSM 151109B-31; ID RCB: 2015-A01247) and participants gave their written informed consent.

### 2.1. Participants

Two male 22-year-old monozygotic twins with 22q11.2DS participated in the study. They were carefully selected because of the rare phenotypic discordance considering psychiatric manifestations. An experienced psychiatrist examined both twins according to DSM-5 criteria axis 1 and completed Positive And Negative Syndrome Scale (PANSS) for schizophrenia (Kay et al., 1987). Diagnosis of 22q11.2DS was confirmed by complete genomic hybridization (CHG-Array) and verified in both patients by fluorescent in situ hybridization (FISH) revealing an identical heterozygous de novo 2.6 Mb deletion in chromosomal region 22q11.21. The cytogenetic analysis also revealed a 1.4 Mb homozygous deletion in chromosomal region Xp22.31 including the STS gene. This recurrent deletion is responsible for X-chromosome-linked ichthyosis. Accordingly, the two twins demonstrated dry and scaly skin. Some reports indicated that this deletion might also be associated with attention-deficit hyperactivity and autism spectrum disorder (Baek and Aypar, 2017; Brookes et al., 2008; Kent et al., 2008), but neither of the two twins reached the DSM-5 criteria for these comorbidities. Anatomical brain MRI data were unremarkable.

The clinical histories of the twins were highly similar. They were born by caesarean delivery after 36 weeks of gestation and have been educated together in similar conditions. They are still living with their parents. They displayed mild 22q11.2DS dysmorphic facial features without velopharyngeal insufficiency. They presented with neither immune deficiency nor hypocalcemia. Twin1 exhibited a common arterial trunk during the neonatal period that required a surgery without complication and Twin2 was asymptomatic. From a neurodevelopmental perspective, they presented with a mild delay concerning walking and speech and were described as 'turbulent' children without fulfilling DSM-5 criteria for attention-deficit hyperactivity disorder. They received speech, orthoptic, and psychomotor therapies during their childhood. They encountered learning problems at school, but both were capable of pursuing their training and graduated with a vocational baccalaureate. The extensive neuropsychological examination concludes to a borderline intellectual functioning with a similar profile in both twins. Basic shape perceptions seemed efficient while spatial perceptions were impaired. The twins also had consequent visuo-constructive disabilities associated with a moderate dysexecutive syndrome. Working memory abilities were equally accurate, but learning curves were reduced and long-term recall abilities impaired (for details, see Table 1).

At the time of testing, the psychiatric presentation of each twin only differed regarding schizophrenic symptoms. Twin1 presented with schizophrenia according to DSM-5 criteria. He displayed delusions, suspiciousness, hostility, blunted affect, emotional withdrawal, lack of spontaneity, stereotyped thinking, active social avoidance, and anxiety. Twin2 presented with an isolated blunted affect without psychotic symptoms. Discordant clinical observations between both twins were confirmed by the PANSS scores (for details, see Table 1). Neither has a history of antipsychotic treatment nor received drug during the testing period.

### 2.2. Experimental procedure

Two measures were used to assess emotional face processing.

#### 2.2.1. TREF test

The TREF test (Gaudelus et al., 2015) assesses the ability to recognize six basic emotions (joy, anger, sadness, fear, disgust, and contempt). Fifty-four emotional faces are presented for 10 s each with nine levels of intensity ranging from 20% to 100%. Participants have to choose orally the correct answer among the 6 written labels of basic emotions. No time limit for responding is applied. This test provides a global percentage of emotion recognition and a threshold of intensity at which emotions are correctly recognized. Detailed procedure and score

**Table 1**  
Behavioural and cognitive profile of the twins suffering from 22q11.2DS (raw score).

	Twin 1	Twin 2
<b>Schizophrenic symptoms</b>		
PANSS - positive symptoms score	20	8
PANSS - negative symptoms score	24	14
PANSS - general symptoms score	39	22
PANSS - total score	83	44
<b>Global cognitive abilities</b>		
WAIS IV - verbal comprehension index	75	77
WAIS IV - perceptual reasoning index	62 *	70
WAIS IV - processing speed index	77	83
WAIS IV - working memory index	84	81
WAIS IV - full scale intellectual quotient	68 * <sup>†</sup>	72
<b>Visuo-spatial functions</b>		
VOSP - screening test (total score)	20	20
VOSP - incomplete letters (total score)	20	19
BORB - foreshortened view task (total score)	24	20
Benton judgment of line orientation test (total score)	14 *	12 *
Rey complex figure copy test (total score)	19.5 *	25 *
<b>Attentional and executive functions</b>		
D2 - concentration performance index	135	135
TMT - flexibility index (time)	49	43
TMT - flexibility index (errors)	0	0
Stroop test - interference index (time)	36	24
Stroop test - interference index (errors)	4 *	10 *
Brixton spatial anticipation test (errors)	22 *	21 *
<b>Memory</b>		
WAIS IV - digit span test (total score)	23	23
WMS III - spatial memory test (total score)	14	14
CVLT - learning (total score)	42*	46 *
CVLT - long term recall (total score)	8	9

PANSS = Positive And Negative Symptoms Scale (Kay et al., 1987); WAIS IV = Wechsler Adult Intelligence Scale fourth edition (Wechsler, 2008); VOSP = Visual Object and Space Perception Battery (Warrington, 1991); Birmingham Object Recognition battery (Riddoch and Humphreys, 1993); Benton judgment of line orientation test (Benton et al., 1978); Rey complex figure copy test (Rey, 1960); D2 (Brickenkamp and Zillmer, 1998); TMT = Trail Making Test (Godefroy and GREFEX, 2008); Stroop test (Godefroy and GREFEX, 2008); Brixton spatial anticipation test (Godefroy and GREFEX, 2008); WMS III = Wechsler memory Scale third edition (Wechsler, 2001); CVLT = California Verbal Learning Test (Delis et al., 1987). Asterisks (\*) represent scores which were two standard deviations or more from the normative sample mean.

<sup>†</sup> The full scale intellectual quotient must be carefully interpreted since differences between index scores are statistically significant (the perceptual reasoning index is lower than the three others indexes).

computation are available in Gaudelus et al., 2015 and the supplementary file.

### 2.2.2. Facial expression perception (FEP) measurement

A fast periodic visual stimulation coupled with EEG was used to implicitly measure the detection of brief changes of facial expression (anger, disgust, fear, happiness and sadness) at different intensity levels (20%, 60%, 100%). This paradigm was adapted from previous studies (Leleu et al., 2018, 2019), and details of the procedure and data acquisition are available in the supplementary file. Briefly, neutral faces were presented at a base rate of 6 Hz and expressive faces were introduced at a lower rate of 1.2 Hz (i.e., every 5 stimuli). This frequency-tagging approach allows dissociating two brain responses: the first one elicited at 6 Hz and harmonics (i.e., integer multiples) reflects the general visual processing of the rapid stream of stimulation; the second one elicited at 1.2 Hz and harmonics precisely indexes the discrimination of facial expression from neutrality. Participants performed a non-periodic orthogonal task (i.e., unrelated to facial expression perception) asking them to detect shape-changes (i.e., to square) of a fixation circle continuously presented just below the eyes of the face stimuli.

## 2.3. Data processing and statistical analyses

### 2.3.1. TREF data analysis

The global percentage of emotion recognition and the threshold of intensity of both patients were compared to 38 healthy controls (men without history of psychiatric or genetic disease, mean age  $\pm$  standard error:  $21.47 \pm 1.84$ ) (unpublished data) by using the Crawford and Howell's adapted *t*-test (Crawford and Howell, 1998) ( $p < .05$ , two-tailed). Normality of the sample was tested thanks to Shapiro-Wilk normality test ( $p < .05$ ).

### 2.3.2. FEP measurement data analyses

For the orthogonal behavioural task, percentage of correct detection occurring between 150 and 1000 ms was calculated to ensure that both twins paid full attention to the screen during stimulation. For EEG data, detailed preprocessing and analysis steps are described in the supplementary file. Briefly, EEG amplitude spectra were analysed in the frequency domain using fast Fourier transform. For both general visual and facial expression change responses, the signal amplitude was summed across harmonics, and noise amplitude was estimated from 20 surrounding frequency bins. Corrected amplitude of neural responses was quantified by subtracting mean noise from the signal amplitude. *Z*-scores were also computed to estimate the significance of the responses (signal minus mean noise divided by the standard deviation of the noise). To compare both responses between twins, the difference between their summed uncorrected amplitudes was calculated and *Z*-scores were computed. An exploratory analysis was conducted across 48 posterior electrodes since previous studies revealed a posterior topography for both brain responses measured with a similar design (Dzhelyova et al., 2017; Leleu et al., 2018). The *Z*-score significance threshold was adjusted using Bonferroni correction for multiple comparisons between electrodes ( $Z > 3.08$ ,  $p < .001$ , one-tailed, signal  $>$  noise for the significance of each brain response;  $Z > 3.28$  or  $< -3.28$ ,  $p < .001$ , two-tailed for the significance of the difference between twins).

According to previous studies, the expression-change response is not significant for low-intensity facial expressions in both healthy and 22q11.2DS participants (Leleu et al., 2018, 2019). Consequently, separate analyses were performed for the 20% expression intensity (referred to as low intensity condition), and for 60% and 100% combined (referred to as high intensity condition). Analysis of the general visual response was performed on the average across expression intensities. To increase signal-to-noise ratio, both responses were averaged across emotions.

## 3. Results

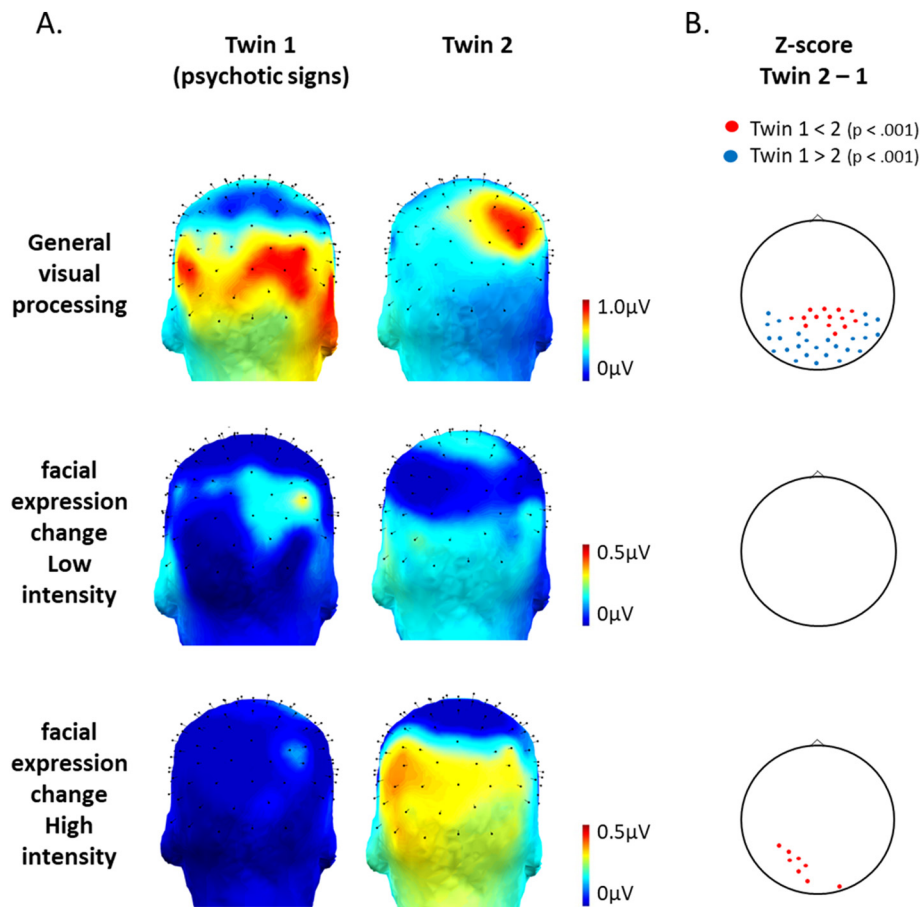
### 3.1. TREF test

Data of the healthy control group follow a normal distribution (global recognition score:  $W = 0.97$ ,  $p = .30$ ; threshold of intensity:  $W = 0.96$ ,  $p = .10$ ). The TREF test indicated that both twins exhibited lower global recognition scores than controls (Controls:  $72.47\% \pm 7.64$ ; Twin1:  $55.56\%$ ,  $t(27) = -2.17$ ,  $p < .05$ ; Twin2:  $48.15\%$ ,  $t(27) = -3.13$ ,  $p < .01$ ) and higher thresholds of intensity at which emotions are recognized (Controls:  $46.47\% \pm 7.78$ ; Twin1:  $66.67\%$ ,  $t(27) = 2.55$ ,  $p < .02$ ; Twin2:  $78.33\%$ ,  $t(27) = -4.02$ ,  $p < .001$ ). Further details are provided in the supplementary file.

### 3.2. FEP measurement

For the orthogonal behavioural task (i.e., shape-change detection of the fixation circle) performed during EEG recordings, results were 89.4% correct responses for Twin1 and 95.0% correct responses for Twin2. These results ensure that both paid full attention to the visual stimulation.





**Fig. 1.** A. 3D-topographical maps (posterior view) of summed corrected amplitudes for the general visual response (top) and for the facial expression specific response (bottom) at low and high intensities for Twin1 (with psychotic symptoms) and Twin2 (without psychotic symptoms). B. Localization of the electrodes for which the brain responses significantly differ between twins.

Similarly, the general visual response in EEG was significant over all 48 electrodes for both twins ( $Z_s > 3.08$ ,  $p_s < 0.001$ ). The direct comparison between twins for the general visual response reached significance for 40 electrodes. The response was larger for Twin 1 over 14 electrodes ( $Z_s < -4.15$ ,  $p_s < 0.001$ ), and the reverse pattern was found over another 26 electrodes ( $Z_s > 3.33$ ,  $p_s < 0.001$ ).

The expression-change brain response to low-intensity facial expressions did not reach significance for either twin ( $Z_s < 1.81$ ,  $p_s > 0.04$ ) and did not significantly differ between twins ( $Z_s < 2.00$ ,  $p_s > 0.045$ ). Importantly, the response to high-intensity facial expressions did not reach significance over any electrode for Twin1 ( $Z_s < 0.88$ ,  $p_s > 0.19$ ) while it reached significance over 11 electrodes for Twin2 ( $Z_s > 3.23$ ,  $p_s < 0.001$ ). Accordingly, the response to high-intensity facial expressions was lower for Twin1 than Twin2 over 8 electrodes ( $Z_s > 3.39$ ,  $p_s < 0.001$ ), in line with the significant expression-change response found only for Twin 2.

Details of the EEG results are provided in Fig. 1 and in the supplementary file.

#### 4. Discussion

The present study aimed at better circumscribing the neurocognitive endophenotype of psychotic symptoms by considering confounding factors and using a twin study with an experimental paradigm that specifically measures facial emotion perception at the individual level. The results of this exploratory study support the association between psychotic symptoms and impaired facial expression perception.

As hypothesized, the classical behavioural task of face recognition (TREF test) failed to be clearly associated with psychotic symptoms in Twin1 in comparison with Twin2 since their scores were both impaired in comparison with the control sample. On the contrary, the FEP

measurement showed that the twin suffering from psychotic symptoms (Twin1) did not detect facial expression changes while the other (Twin2) did, in line with previous evidence showing a relationship between positive symptoms of psychosis and such automatic perception of facial expression changes (Leleu et al., 2019). Direct comparison between the twins confirmed that the EEG response to emotional faces was lower in Twin1 than Twin2.

It could be possible that this impairment represents one aspect of a broader difficulty to detect some pattern changes within visual stimuli irrespective of social content, as defined in the hypothesis of a coarser resolution of spatiotemporal information in 22q11.2DS (Simon, 2008). This interesting alternative interpretation could adequately apply to the present observation since facial expression changes were displayed briefly. Further studies are needed to explore this option. However, it is worth noting that the general visual response to the rapid stream of stimulation was significant in both participants indicating that stimulus luminance, contrast and size are perceived. The high accuracy for both twins in the orthogonal task also indicates that they perceived the target. This could lead to discard any interpretation in terms of reduced global visual sensitivity. Direct comparisons between the twins also revealed a distinct topographical pattern. Future studies should investigate whether this different topography between twins could also be associated with the presence of psychotic symptoms.

Either way, the difficulties of Twin1 in the FEP measurement were thus specific to the visual processing of a change of facial expression from a neutral face. There is therefore discordance between explicit emotion labelling tasks and implicit facial expression perception, suggesting that facial expression perception is closely related to psychotic symptoms whereas explicit emotion recognition is a more widespread phenotype in 22q11.2DS individuals irrespective of their psychotic status. In other words, the ability to explicitly attribute an emotion to

expressive faces seems generally impaired in 22q11.2DS while only individuals with psychotic symptoms may additionally (and even primarily) suffer from difficulties in perceiving distinct facial expressions. Since the brain response to expressive faces measured in the present study is exempt from explicit processes, it appears to be a reliable potential endophenotype of psychotic symptoms (Leleu et al., 2019). This marker could be appropriately used in future genetic studies as well as in clinical care strategies, in place of standard behavioural measures that provide only moderate specificity for psychotic symptoms. Admittedly, one limitation of the present study is the lack of longitudinal data. No assumption can be made on any causal relationship between facial expression perception and psychotic symptoms emergence. Another limitation would be that the mere comparison of twins can be considered as a fixed effect analysis (psychotic vs. non-psychotic) that hardly generalizes to the whole 22q11.2DS population. However, since the present findings are concordant with a previous study using the same approach without fixing the “psychotic symptoms” parameter (Leleu et al., 2019), we remain confident about the generalizability of our observations.

Some reports have previously challenged the idea of a specific social cognitive dysfunction associated with the occurrence of psychotic manifestations. Global cognitive decline and/or cognitive inflexibility were proposed as predictors of psychotic symptom onset in 22q11.2DS (Antshel et al., 2016; Schneider et al., 2014; Tang and Gur, 2017; Vorstman et al., 2015; Weinberger et al., 2016). There is much evidence across various clinical conditions (including 22q11.2DS) that global cognitive and/or executive capacity may partly explain the performance heterogeneity in social cognitive tasks (Norkett et al., 2017; Wood and Worthington, 2017). Nevertheless, global intellectual abilities, executive and general visuo-spatial functions presumably did not account for psychotic symptoms in our study since cognitive profiles are highly similar across twins. The present results are rather coherent with recent data that failed to find evidence for general cognitive ability decrement in correlation with psychotic symptoms in 22q11.2DS (Chawner et al., 2017; Niarchou et al., 2014). They also support the recent view of a clear relationship between social cognitive impairment and psychotic symptoms (Antshel et al., 2016; Badoud et al., 2017; Jalbrzikowski et al., 2012, 2014; Weinberger et al., 2016).

The etiology of the incomplete penetrance of psychosis in 22q11.2DS is a highly critical question. Regarding genetic explanations, several hypotheses have been raised, ranging from additional genomic mutation outside of the 22q region (Balan et al., 2014; Bassett et al., 2017; Toyosima et al., 2011) to epigenetic factors (Cirillo et al., 2014; Singh et al., 2002; Starnawska et al., 2017), without forgetting the potential role of the other allele and especially COMT polymorphisms (Gothelf et al., 2007, 2014; Guipponi et al., 2017; Merico et al., 2015; Thompson et al., 2017) or intergenic noncoding RNA genes (Merico et al., 2015). A more integrative model suggests that psychotic symptoms may occur from genetic risk combined with negative life events, traumatic experiences, and/or attachment disorder (Biswas and Furniss, 2016). Although it cannot definitely rule out or validate these potential explanations, the present study might reasonably highlight some of them. The case of the two monozygotic twins discordant for psychotic symptoms also tends to discard the role of an additional genomic event and drives us to focus on epigenetic and transcriptomic investigations. This view was recently supported by a study that correlated long term mental disorder in 22q11.2DS with differential DNA methylation at birth (Starnawska et al., 2017). However, this hypothesis raises the issue of epigenome changes (Toraño et al., 2016) in monozygotic twins who have grown up together. The only known environmental difference between the twins is a cardiac surgery. Nevertheless, previous data did not find a substantial link between congenital heart disease and further psychiatric symptom onset in 22q11.2DS (Yi et al., 2014). Further investigations are thus required.

In any case, the experimental design of the present study – that is, the combination of a specific electrophysiological measure of a

cognitive process and the selection of patients that leads to comparable environmental and genomic factors – provides a unique opportunity to bring forward the discussion on the neurocognitive endophenotype of psychotic symptoms. The present data ideally should be confirmed by replication studies. In practice, the scarcity of 22q11.2DS restricts the possibility of studying a large cohort of monozygotic twins with heterogeneous clinical presentation of psychotic symptoms.

## Funding

This work was supported by the Scientific Committee of Research of the Hospital ‘Le Vinatier’ (CSR-02); the “Conseil Régional Bourgogne Franche-Comté” (PARI); the European Funding for Regional Economic Development (FEDER); and the French “Investissements d’Avenir” program (ANR-15-IDEX-03). The authors declare no other conflict of interest.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.nicl.2019.101987>.

## References

- Antshel, K.M., Fremont, W., Ramanathan, S., Kates, W.R., 2016. Predicting cognition and psychosis in Young adults with 22q11.2 deletion syndrome. *Schizophr. Bull.* <https://doi.org/10.1093/schbul/sbw135>.
- Azuma, R., Deeley, Q., Campbell, L.E., Daly, E.M., Giampietro, V., Brammer, M.J., Murphy, K.C., Murphy, D.G., 2015. An fMRI study of facial emotion processing in children and adolescents with 22q11.2 deletion syndrome. *J. Neurodev. Disord.* 7 (1). <https://doi.org/10.1186/1866-1955-7-1>.
- Badoud, D., Schneider, M., Menghetti, S., Glaser, B., Debbané, M., Eliez, S., 2017. Understanding others: a pilot investigation of cognitive and affective facets of social cognition in patients with 22q11.2 deletion syndrome (22q11DS). *J. Neurodev. Disord.* 9 (35). <https://doi.org/10.1186/s11689-017-9216-7>.
- Baek, W.S., Aypar, U., 2017. Neurological manifestations of X-linked Ichthyosis: case report and review of the literature. *Case Rep. Genet.* 2017, 1–5. <https://doi.org/10.1155/2017/9086408>.
- Balan, S., Iwayama, Y., Toyota, T., Toyoshima, M., Maekawa, M., Yoshikawa, T., 2014. 22q11.2 deletion carriers and schizophrenia-associated novel variants. *Br. J. Psychiatry* 204, 398–399. <https://doi.org/10.1192/bjp.bp.113.138420>.
- Bassett, A.S., Lowther, C., Merico, D., Costain, G., Chow, E.W.C., van Amelsvoort, T., McDonald-McGinn, D., Gur, R.E., Swillen, A., Van den Bree, M., Murphy, K., Gothelf, D., Bearden, C.E., Eliez, S., Kates, W., Philip, N., Sashi, V., Campbell, L., Vorstman, J., Cubells, J., Repetto, G.M., Simon, T., Boot, E., Heung, T., Evers, R., Vingerhoets, C., van Duin, E., Zackai, E., Vergaelen, E., Devriendt, K., Vermeesch, J.R., Owen, M., Murphy, C., Michaelovsky, E., Kushan, L., Schneider, M., Fremont, W., Busa, T., Hooper, S., McCabe, K., Duijff, S., Isaev, K., Pellecchia, G., Wei, J., Gazzellone, M.J., Scherer, S.W., Emanuel, B.S., Guo, T., Morrow, B.E., Marshall, C.R., International 22q11.2DS Brain and Behavior Consortium, 2017. Rare genome-wide copy number variation and expression of schizophrenia in 22q11.2 deletion syndrome. *Am. J. Psychiatry* 174, 1054–1063. <https://doi.org/10.1176/appi.ajp.2017.16121417>.
- Benton, A.L., Varney, N.R., Hamsler, K.D., 1978. Visuospatial judgment. *A clinical test.* *Arch. Neurol.* 35, 364–367.
- Biswas, A.B., Furniss, F., 2016. Cognitive phenotype and psychiatric disorder in 22q11.2 deletion syndrome: a review. *Res. Dev. Disabil.* 53–54, 242–257. <https://doi.org/10.1016/j.ridd.2016.02.010>.
- Boot, E., van Amelsvoort, T.A., M., J., 2012. Neuroimaging correlates of 22q11.2 deletion syndrome: implications for schizophrenia research. *Curr. Top. Med. Chem.* 12, 2303–2313.
- Braun, S., Bridler, R., Müller, N., Schwarz, M.J., Seifritz, E., Weisbrod, M., Zraggen, A., Stassen, H.H., 2017. Inflammatory processes and schizophrenia: two independent lines of evidence from a study of twins discordant and concordant for schizophrenic disorders. *Eur. Arch. Psychiatry Clin. Neurosci.* 267, 377–389. <https://doi.org/10.1007/s00406-017-0792-z>.
- Brickenkamp, R., Zillmer, E., 1998. *d2 Test of Attention*.
- Brookes, K.J., Hawi, Z., Kirley, A., Barry, E., Gill, M., Kent, L., 2008. Association of the steroid sulfatase (STS) gene with attention deficit hyperactivity disorder. *Am. J. Med. Genet. Part B Neuropsychiatr. Genet. Off. Publ. Int. Soc. Psychiatr. Genet.* 147B, 1531–1535. <https://doi.org/10.1002/ajmg.b.30873>.
- Campbell, L.E., McCabe, K.L., Melville, J.L., Strutt, P.A., Schall, U., 2015. Social cognition dysfunction in adolescents with 22q11.2 deletion syndrome (velo-cardio-facial syndrome): relationship with executive functioning and social competence/functioning. *J. Intellect. Disabil. Res.* 59, 845–859. <https://doi.org/10.1111/jir.12183>.
- Castellani, C.A., Melka, M.G., Gui, J.L., Gallo, A.J., O'Reilly, R.L., Singh, S.M., 2017. Post-zygotic genomic changes in glutamate and dopamine pathway genes may explain discordance of monozygotic twins for schizophrenia. *Clin. Transl. Med.* 6 (43). <https://doi.org/10.1186/s40169-017-0174-1>.
- Chawner, S.J.R.A., Doherty, J.L., Moss, H., Niarchou, M., Walters, J.T.R., Owen, M.J., van den Bree, M.B.M., 2017. Childhood cognitive development in 22q11.2 deletion syndrome: case-control study. *Br. J. Psychiatry* 211, 223–230. <https://doi.org/10.1192/bjp.2016.201>.

- 1192/bjp.bp.116.195651.
- Chung, J.H., Cai, J., Suskin, B.G., Zhang, Z., Coleman, K., Morrow, B.E., 2015. Whole-genome sequencing and integrative genomic analysis approach on two 22q11.2 deletion syndrome family trios for genotype to phenotype correlations. *Hum. Mutat.* 36, 797–807. <https://doi.org/10.1002/humu.22814>.
- Cirillo, E., Giardino, G., Gallo, V., Puliafito, P., Azzari, C., Bacchetta, R., Cardinale, F., Cicalese, M.P., Consolini, R., Martino, S., Martire, B., Molinatto, C., Plebani, A., Scarano, G., Soresina, A., Cancrini, C., Rossi, P., Digilio, M.C., Pignata, C., 2014. Intergenerational and intrafamilial phenotypic variability in 22q11.2 deletion syndrome subjects. *BMC Med. Genet.* 15 (1). <https://doi.org/10.1186/1471-2350-15-1>.
- Crawford, J.R., Howell, D.C., 1998. Comparing an individual's test score against norms derived from small samples. *Clin. Neuropsychol.* 12, 482–486. <https://doi.org/10.1076/clin.12.4.482.7241>.
- Delis, D., Kramer, J., Kaplan, E., Ober, B., 1987. *CVLT, California Verbal Learning Test: Adult Version: Manual*.
- Dzhelyova, M., Jacques, C., Rossion, B., 2017. At a single glance: fast periodic visual stimulation uncovers the Spatio-temporal dynamics of brief facial expression changes in the human brain. *Cereb. Cortex N. Y. N 1991* (27), 4106–4123. <https://doi.org/10.1093/cercor/bhw223>.
- Gaudelus, B., Virgile, J., Peyroux, E., Leleu, A., Baudouin, J.-Y., Franck, N., 2015. [Measuring impairment of facial affects recognition in schizophrenia. Preliminary study of the facial emotions recognition task (TREF)]. *L'Encephale*. 41. pp. 251–259. <https://doi.org/10.1016/j.encep.2014.08.013>.
- Godefroy, O., GREFEX, 2008. Fonctions exécutives et pathologies neurologiques et psychiatriques. In: Solal (Ed.), *Évaluation en Pratique Clinique*. Marseille.
- Goodship, J., Cross, I., Scambler, P., Burn, J., 1995. Monozygotic twins with chromosome 22q11 deletion and discordant phenotype. *J. Med. Genet.* 32, 746–748.
- Gothelf, D., Feinstein, C., Thompson, T., Gu, E., Penniman, L., Van Stone, E., Kwon, H., Eliez, S., Reiss, A.L., 2007. Risk factors for the emergence of psychotic disorders in adolescents with 22q11.2 deletion syndrome. *Am. J. Psychiatry* 164, 663–669. <https://doi.org/10.1176/ajp.2007.164.4.663>.
- Gothelf, D., Law, A.J., Frisch, A., Chen, J., Zarchi, O., Michaelovsky, E., Ren-Patterson, R., Lipska, B.K., Carmel, M., Kolachana, B., Weizman, A., Weinberger, D.R., 2014. Biological effects of COMT haplotypes and psychosis risk in 22q11.2 deletion syndrome. *Biol. Psychiatry* 75, 406–413. <https://doi.org/10.1016/j.biopsych.2013.07.021>.
- Guipponi, M., Santoni, F., Schneider, M., Gehrig, C., Bustillo, X.B., Kates, W.R., Morrow, B., Armando, M., Vicari, S., Sloan-Béna, F., Gagnebin, M., Shashi, V., Hooper, S.R., Eliez, S., Antonarakis, S.E., 2017. No evidence for the presence of genetic variants predisposing to psychotic disorders on the non-deleted 22q11.2 allele of VCFS patients. *Transl. Psychiatry* 7, e1039. <https://doi.org/10.1038/tp.2016.258>.
- Gur, R.E., Calkins, M.E., Gur, R.C., Horan, W.P., Nuechterlein, K.H., Seidman, L.J., Stone, W.S., 2006. The consortium on the genetics of schizophrenia: neurocognitive Endophenotypes. *Schizophr. Bull.* 33, 49–68. <https://doi.org/10.1093/schbul/sbl055>.
- Halder, A., Jain, M., Chaudhary, I., Varma, B., 2012. Chromosome 22q11.2 microdeletion in monozygotic twins with discordant phenotype and deletion size. *Mol. Cytogenet.* 5, 13. <https://doi.org/10.1186/1755-8166-5-13>.
- Jalbrzikowski, M., Carter, C., Senturk, D., Chow, C., Hopkins, J.M., Green, M.F., Galván, A., Cannon, T.D., Bearden, C.E., 2012. Social cognition in 22q11.2 microdeletion syndrome: relevance to psychosis? *Schizophr. Res.* 142, 99–107. <https://doi.org/10.1016/j.schres.2012.10.007>.
- Jalbrzikowski, M., Villalon-Reina, J.E., Karlsgodt, K.H., Senturk, D., Chow, C., Thompson, P.M., Bearden, C.E., 2014. Altered white matter microstructure is associated with social cognition and psychotic symptoms in 22q11.2 microdeletion syndrome. *Front. Behav. Neurosci.* 8 (393). <https://doi.org/10.3389/fnbeh.2014.00393>.
- Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr. Bull.* 13, 261–276.
- Kent, L., Emerton, J., Bhadravathi, V., Weisblatt, E., Pasco, G., Willatt, L.R., McMahon, R., Yates, J.R.W., 2008. X-linked ichthyosis (steroid sulfatase deficiency) is associated with increased risk of attention deficit hyperactivity disorder, autism and social communication deficits. *J. Med. Genet.* 45, 519–524. <https://doi.org/10.1136/jmg.2008.057729>.
- Leleu, A., Saucourt, G., Rigard, C., Chesnoy, G., Baudouin, J.-Y., Rossi, M., Edery, P., Franck, N., Demily, C., 2016. Facial emotion perception by intensity in children and adolescents with 22q11.2 deletion syndrome. *Eur. Child Adolesc. Psychiatry* 25, 297–310. <https://doi.org/10.1007/s00787-015-0741-1>.
- Leleu, A., Dzhelyova, M., Rossion, B., Brochard, R., Durand, K., Schaal, B., Baudouin, J.-Y., 2018. Tuning functions for automatic detection of brief changes of facial expression in the human brain. *NeuroImage* 179, 235–251. <https://doi.org/10.1016/j.neuroimage.2018.06.048>.
- Leleu, A., Favre, E., Yaïlian, A., Fumat, H., Klammer, J., Amado, I., Baudouin, J.-Y., Franck, N., Demily, C., 2019. An implicit and reliable neural measure quantifying impaired visual coding of facial expression: evidence from the 22q11.2 deletion syndrome. *Transl. Psychiatry* 9 (67). <https://doi.org/10.1038/s41398-019-0411-z>.
- Liu-Shuang, J., Norcia, A.M., Rossion, B., 2014. An objective index of individual face discrimination in the right occipito-temporal cortex by means of fast periodic oddball stimulation. *Neuropsychologia* 52, 57–72. <https://doi.org/10.1016/j.neuropsychologia.2013.10.022>.
- McCabe, K.L., Marlin, S., Cooper, G., Morris, R., Schall, U., Murphy, D.G., Murphy, K.C., Campbell, L.E., 2016. Visual perception and processing in children with 22q11.2 deletion syndrome: associations with social cognition measures of face identity and emotion recognition. *J. Neurodev. Disord.* 8, 30. <https://doi.org/10.1186/s11689-016-9164-7>.
- Merico, D., Zarrei, M., Costain, G., Ogura, L., Alipanahi, B., Gazzellone, M.J., Butcher, N.J., Thiruvahindrapuram, B., Nalpathamkalam, T., Chow, E.W.C., Andrade, D.M., Frey, B.J., Marshall, C.R., Scherer, S.W., Bassett, A.S., 2015. Whole-genome sequencing suggests schizophrenia risk mechanisms in humans with 22q11.2 deletion syndrome. *G3 Bethesda Md* 5, 2453–2461. <https://doi.org/10.1534/g3.115.021345>.
- Niarchou, M., Zammit, S., van Goozen, S.H.M., Thapar, A., Tierling, H.M., Owen, M.J., Van Den Bree, M.B.M., 2014. Psychopathology and cognition in children with 22q11.2 deletion syndrome. *Br. J. Psychiatry* 204, 46–54. <https://doi.org/10.1192/bjp.bp.113.132324>.
- Nishioka, K., Bundo, M., Ueda, J., Yoshikawa, A., Nishimura, F., Sasaki, T., Kakiuchi, C., Kasai, K., Kato, T., Iwamoto, K., 2018. Identification of somatic mutations in monozygotic twins discordant for psychiatric disorders. *NPJ Schizophr.* 4 (7). <https://doi.org/10.1038/s41537-018-0049-5>.
- Norcia, A.M., Appelbaum, L.G., Ales, J.M., Cottareau, B.R., Rossion, B., 2015. The steady-state visual evoked potential in vision research: a review. *J. Vis.* 15, 4. <https://doi.org/10.1167/15.6.4>.
- Norkett, E.M., Lincoln, S.H., Gonzalez-Heydrich, J., D'Angelo, E.J., 2017. Social cognitive impairment in 22q11 deletion syndrome: a review. *Psychiatry Res.* 253, 99–106. <https://doi.org/10.1016/j.psychres.2017.01.103>.
- Owen, M.J., Doherty, J.L., 2016. What can we learn from the high rates of schizophrenia in people with 22q11.2 deletion syndrome? *World Psychiatry* 15, 23–25. <https://doi.org/10.1002/wps.20274>.
- Poncet, F., Baudouin, J.-Y., Dzhelyova, M.P., Rossion, B., Leleu, A., 2019. Rapid and automatic discrimination between facial expressions in the human brain. *Neuropsychologia* 129, 47–55. <https://doi.org/10.1016/j.neuropsychologia.2019.03.006>.
- Rey, A., 1960. Test de la figure complexe de Rey.
- Riddoch, J., Humphreys, G., 1993. *BORB: Birmingham Object Recognition Battery*.
- Sabharwal, A., Kotov, R., Szekely, A., Leung, H.-C., Barch, D.M., Mohanty, A., 2017. Neural markers of emotional face perception across psychotic disorders and general population. *J. Abnorm. Psychol.* 126, 663–678. <https://doi.org/10.1037/abn0000279>.
- Schneider, M., Schaefer, M., Mutlu, A., Menghetti, S., Glaser, B., Debbané, M., Eliez, S., 2014. Clinical and cognitive risk factors for psychotic symptoms in 22q11.2 deletion syndrome: a transversal and longitudinal approach. *Eur. Child Adolesc. Psychiatry* 23, 425–436. <https://doi.org/10.1007/s00787-013-0469-8>.
- Simon, T.J., 2008. A new account of the neurocognitive foundations of impairments in space, time and number processing in children with chromosome 22q11.2 deletion syndrome. *Dev. Disabil. Res. Rev.* 14, 52–58.
- Singh, S.M., Murphy, B., O'Reilly, R., 2002. Monozygotic twins with chromosome 22q11 deletion and discordant phenotypes: updates with an epigenetic hypothesis. *J. Med. Genet.* 39, e71.
- Starnawska, A., Hansen, C.S., Sparso, T., Mazin, W., Olsen, L., Bertalan, M., Buil, A., Bybjerg-Grauholm, J., Bækvad-Hansen, M., Hougaard, D.M., Mortensen, P.B., Pedersen, C.B., Nyegaard, M., Werge, T., Weinsheimer, S., 2017. Differential DNA methylation at birth associated with mental disorder in individuals with 22q11.2 deletion syndrome. *Transl. Psychiatry* 7, e1221. <https://doi.org/10.1038/tp.2017.181>.
- Tang, S.X., Gur, R.E., 2017. Longitudinal perspectives on the psychosis spectrum in 22q11.2 deletion syndrome. *Am. J. Med. Genet. A*. <https://doi.org/10.1002/ajmg.a.38500>.
- Thompson, C.A., Karelis, J., Middleton, F.A., Gentile, K., Coman, L.L., Radoeva, P.D., Mehta, R., Fremont, W.P., Antshel, K.M., Faraone, S.V., Kates, W.R., 2017. Associations between neurodevelopmental genes, neuroanatomy, and ultra high risk symptoms of psychosis in 22q11.2 deletion syndrome. *Am. J. Med. Genet. Part B Neuropsychiatr. Genet. Off. Publ. Int. Soc. Psychiatr. Genet.* 174, 295–314. <https://doi.org/10.1002/ajmg.b.32515>.
- Toraño, E.G., García, M.G., Fernández-Morera, J.L., Niño-García, P., Fernández, A.F., 2016. The impact of external factors on the Epigenome: *In Utero* and over lifetime. *Biomed. Res. Int.* 2016, 1–17. <https://doi.org/10.1155/2016/2568635>.
- Toyosima, M., Maekawa, M., Toyota, T., Iwayama, Y., Arai, M., Ichikawa, T., Miyashita, M., Arinami, T., Itokawa, M., Yoshikawa, T., 2011. Schizophrenia with the 22q11.2 deletion and additional genetic defects: case history. *Br. J. Psychiatry* 199, 245–246. <https://doi.org/10.1192/bjp.bp.111.093849>.
- Vorstman, J.A.S., Breetvelt, E.J., Duijff, S.N., Eliez, S., Schneider, M., Jalbrzikowski, M., Armando, M., Vicari, S., Shashi, V., Hooper, S.R., Chow, E.W.C., Fung, W.L.A., Butcher, N.J., Young, D.A., McDonald-McGinn, D.M., Vogels, A., van Amelsvoort, T., Gothelf, D., Weinberger, R., Weizman, A., Klaassen, P.W.J., Kooops, S., Kates, W.R., Antshel, K.M., Simon, T.J., Ousley, O.Y., Swillen, A., Gur, R.E., Bearden, C.E., Kahn, R.S., Bassett, A.S., 2015. Cognitive decline preceding the onset of psychosis in patients with 22q11.2 deletion syndrome. *JAMA Psychiatry* 72, 377–385. <https://doi.org/10.1001/jamapsychiatry.2014.2671>.
- Warrington, E., 1991. *The Visual Object and Space Perception Battery: VOSP*.
- Wechsler, D., 2001. In: *ECPA (Ed.), MEM-III Echelle clinique de mémoire - troisième édition*.
- Wechsler, D., 2008. *WAIS-IV Echelle d'intelligence de Wechsler pour adultes - 4e édition*. ECPA.
- Weinberger, R., Yi, J., Calkins, M., Guri, Y., McDonald-McGinn, D.M., Emanuel, B.S., Zackai, E.H., Ruparel, K., Carmel, M., Michaelovsky, E., Weizman, A., Gur, R.C., Gur, R.E., Gothelf, D., 2016. Neurocognitive profile in psychotic versus nonpsychotic individuals with 22q11.2 deletion syndrome. *Eur. Neuropsychopharmacol.* <https://doi.org/10.1016/j.euroneuro.2016.08.003>.
- Wood, R.L., Worthington, A., 2017. Neurobehavioral abnormalities associated with executive dysfunction after traumatic brain injury. *Front. Behav. Neurosci.* 11 (195). <https://doi.org/10.3389/fnbeh.2017.00195>.
- Yi, J.J., Tang, S.X., McDonald-McGinn, D.M., Calkins, M.E., Whinna, D.A., Souders, M.C., Zackai, E.H., Goldmuntz, E., Gaynor, J.W., Gur, R.C., Emanuel, B.S., Gur, R.E., 2014. Contribution of congenital heart disease to neuropsychiatric outcome in school-age children with 22q11.2 deletion syndrome. *Am. J. Med. Genet. Part B Neuropsychiatr. Genet. Off. Publ. Int. Soc. Psychiatr. Genet.* 165B, 137–147. <https://doi.org/10.1002/ajmg.b.32215>.