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ORIGINAL INVESTIGATION

Handedness as a neurodevelopmental marker in schizophrenia: Results from the FACE-SZ cohort

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ABSTRACT

Objectives: High rates of non-right-handedness (NRH) including mixed-handedness have been reported in neurodevelopmental disorders. In schizophrenia (SZ), atypical handedness has been inconsistently related to impaired features. We aimed to determine whether SZ subjects with NRH and mixed-handedness had poorer clinical and cognitive outcomes compared to their counterparts.

Methods: 667 participants were tested with a battery of neuropsychological tests, and assessed for laterality using the Edinburg Handedness Inventory. Clinical symptomatology was assessed. Learning disorders and obstetrical complications were recorded. Biological parameters were explored.

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Results: The prevalence of NRH and mixed-handedness was high (respectively, 42.4% and 34.1%). In the multivariable analyses, NRH was associated with cannabis use disorder ($p = 0.045$). Mixed-handedness was associated with positive symptoms ($p = 0.041$), current depressive disorder ($p = 0.005$)), current cannabis use ($p = 0.024$) and less akathisia ($p = 0.019$). A history of learning disorder was associated with NRH. No association was found with cognition, trauma history, obstetrical complications, psychotic symptoms, peripheral inflammation.
Conclusions: Non-right and mixed-handedness are very high in patients with SZ, possibly reflecting a neurodevelopmental origin. NRH is associated with learning disorders and cannabis use. Mixed-handedness is associated with positive symptoms, current depressive disorder, cannabis use and less akathisia. However, this study did not confirm greater cognitive impairment in these patients.

1. Introduction

The neurodevelopmental hypothesis of schizophrenia (SZ) is supported by various data including potentially increased non-right handedness (NRH) and mixed-handedness in this population. Brain asymmetry, language, and handedness are believed to be very closely tied, although imperfectly (Rodriguez and Waldenström 2008). Handedness is thus a simple way of capturing atypical lateralisation (Barrantes-Vidal et al. 2013) and has been recently shown to be determined in part by both genetic and biological pathways (Satz and Green 1999; Brandler and Paracchini 2014). The frontostriatal monoaminergic circuits implicated in the occurrence of SZ are also lateralised (Klimkeit and Bradshaw 2006). Various hypotheses have been put forward to explain brain asymmetry such as the left hemisphere lag, the left hemisphere being especially vulnerable to insults, and frank differences in hemispheric specialisation (Geschwind and Galaburda 1985). NRH could result from an acute neurodevelopmental impairment (van Dyck et al. 2012; Ho et al. 2017; Wang B et al. 2018) associated with epigenetic processes (due to biological challenges like inflammation/infections for example) that, in addition to genetic factors, are likely to contribute to the SZ pathogenesis. It may thus be reasonably hypothesised that NRH, including mixed-handedness, could be an easy clinical factor to explore abnormal cognitive functions due to brain lateralisation issues (Webb et al. 2013).

NRH has been reported in 8–10% of the general population according to methods and/or samples (Nowakowska et al. 2008; Ravichandran et al. 2017; Darvik et al. 2018). In schizophrenia, several studies have found an increased prevalence of NRH (ranging from 13.1% to 67.7%), with an odds ratio of around 1.5 according to three meta-analyses in comparison to healthy controls or other psychiatric controls (Sommer et al. 2001; Dragovic and Hammond 2005; Hirnstein and Hugdahl 2014). These findings have long corroborated Crow's theory, in which the failure to establish cerebral asymmetry, reflected in hand dominance, is central to schizophrenia (Deep-Soboslay et al. 2010). NRH has been inconsistently related to impaired cognitive functions and other clinical features of SZ. A recent meta-analysis has concluded that increased NRH in SZ was not due to biases like increased men in SZ sex ratio or questionnaires biases (Hirnstein and Hugdahl 2014), renewing the interest in the issue. The latter study also suggested that the association between NRH and schizophrenia might be driven by mixed-handedness, rather than left-handedness. Tran et al (Tran and Voracek 2015) thus hypothesise that the strength of handedness rather than its direction may be linked to SZ. Others also suggest that brain asymmetry may be more strongly associated with mixed- than with left-handedness and may implicate the corpus callosum(Rodriguez and Waldenström 2008). Yet, data are scarce on the clinical and cognitive correlate of mixed-handedness in SZ, whereas around 1 patient in three would present mixed-handedness according to three earlier studies on small samples (prevalence ranging from 36.4% to 43%) (Green et al. 1989; Nelson et al. 1993; Cannon et al. 1995).

Until now, only a handful of studies on handedness in SZ have simultaneously taken into account essential methodological requirements, namely thorough and standardised diagnostic tools, standardised handedness assessment and adequate sample sizes (Deep-Soboslay et al. 2010). To integrate all relevant clinical factors to understand brain asymmetry, the following elements need to be assessed: perinatal history, peripheral inflammation, clinical symptomatology as well as global functioning. They may reflect a shared abnormal neuro-developmental pathway or contribute to defects in cerebral lateralisation (Rodriguez and Waldenström 2008; Llaurens et al. 2009).

Patients with SZ with NRH and mixed-handedness could share other clinical and neurological specificities.

Early studies on small samples suggest that SZ individuals with NRH could share common characteristics such as poorer pre-morbid social adjustment, more neurological soft signs, more tardive dyskinesia, less familial history (McCreadie et al. 1982; Cannon et al. 1995; Browne et al. 2000). These characteristics could indicate a heavier early neurodevelopmental burden, consequence of a defect of cerebral lateralisation such as anomaly of 'wiring'. However, no study has yet examined handedness in learning or language disorders in SZ despite they being associated with abnormal neurodevelopmental patterns and could thus share underlying mechanisms with NRH (Geschwind and Galaburda 1985), and only a few studies examined cognitive functioning in the context of NRH. Some report decreased cognitive performance associated with NRH in SZ in several domains but the small patients' samples cast doubt (Katsanis and Iacono 1989; Faustman et al. 1991; Dragovic et al. 2005), whereas the most recent and largest study ($n = 375$ patients) found no cognitive difference according to handedness(Deep-Soboslay et al. 2010). When focussing on mixed-handedness, we found only one study on a sample of 157 patients reporting no cognitive disadvantage (Dragovic et al. 2005). In comparison, mixed-handedness has been extensively studied in non-clinical samples and associated with psychosis-proneness and deficits in cognitive subtasks (Stefanis et al. 2006; Schürhoff et al. 2008; Barrantes-Vidal et al. 2013).

In this national study, we aimed to determine (i) the prevalence of NRH including mixed-handedness in a large SZ sample; (ii) whether patients with SZ have different clinical, and cognitive profiles when comparing subjects with NRH or mixed-handedness and their counterparts.

2. Material and methods

2.1. Study population

This study is a cross-sectional study based on a national cohort issued from FondaMental Academic Centres of Expertise (FACE), the FACE-SZ cohort (Schürhoff et al. 2015). The FACE-SZ cohort is based on a French national network of 10 Expert Centres. This network was set up by the Fondation FondaMental (www.fondation-fondamental.org) and funded by the French Ministries of Research and of Health in 2007. The cohort and the clinical and cognitive variables have been extensively described (Schürhoff et al. 2015). Stable patients aged above 16 years are referred by their general practitioner or psychiatrist. Diagnoses were carried out by two psychiatrists according to the Structured Clinical Interview for Mental Disorders.

2.1.1. Inclusion criteria

All individuals included were outpatients, living outside the hospital and on stable medication for more than 4 weeks, whereas institutionalised adults were not included. The assessment protocol was approved by the relevant ethical review board (CPP-Ile-de-France IX, 18th January 2010). All data were collected anonymously.

2.2. Data collected

2.2.1. Clinical and sociodemographic measures

Sex, age and educational level were recorded. Illness duration was defined by the number of years between the first psychotic episode (reported by the patient's referring psychiatrist) and the evaluation at the Expert Centre. Duration of untreated psychosis was recorded and defined as the number of years between illness onset and the first antipsychotic medication. These durations were confirmed with the use of hospitalisation records and family interviews. Psychotic and general psychopathology was assessed using the PANSS (Kay et al. 1987). Current depressive symptoms were evaluated with the Calgary Depressive Rating Scale (CDRS) (Bernard et al. 1998). A score $\geq$6 indicates a current depressive episode. Manic symptoms were assessed with YMRS (Young et al. 1978). Global functioning was evaluated with the GAF (Endicott et al. 1976).

Akathisia was measured with the Barnes Akathisia Scale (Barnes 1989), according to the method described in(Berna et al. 2015). Extra-pyramidal side effects were assessed using the SAS (SAS; Simpson and Angus, 1970), and patients were considered to have drug-induced parkinsonism if they had a score $\geq$0.65 (Janno et al. 2005). Abnormal involuntary movements scale (AIMS) was used to assess tardive dyskinesia (Guy 1976).

Ongoing antipsychotic, antidepressant, or mood-stabiliser treatments were recorded. Chlorpromazine equivalent doses (CPZ100eq) were calculated according to the minimum effective dose method (Leucht et al. 2015).

2.2.2. Laterality

Laterality was evaluated by a certified neuropsychologist with the Edinburgh Laterality Inventory (EHI) (Oldfield 1971). This valid and reliable scale gives

scores from −100 (left-handed) to +100 (right-handed). EHI laterality quotient score above +70 defines 'right-handedness' (RH), while a score under 70 are 'left-or mixed-handed', that is, non-right handedness (NRH); and a score between −70 and +70 defines 'mixed-handedness' (Dragovic et al. 2005; Deep-Soboslay et al. 2010). Participants were asked by the examiner to sit with their hands on their thighs and to demonstrate their performance of writing, drawing a picture, throwing a ball, using scissors, brushing their teeth, cutting with a knife, eating with a spoon, striking a match, sweeping with a broom, opening a box, kicking a ball and using a camera or telescope; using the words 'show me how you', without the use of visual cues or prompts.

2.2.3. Neuropsychological measures

Experienced neuropsychologists administered the tests in a fixed order. The standardised test batteries complied with the recommendations issued by the Matrics CCB (Nuechterlein et al. 2008).

- Wechsler Adult Intelligence Scale (WAIS)-3rd Edition provides a measure of general intellectual function in older adolescents and adults in the SZ sample. The seven subtests short form was used and allowed exploration of the following cognitive areas: picture completion (visual exploration and detail perception), Digit-Symbol Coding (visual-motor coordination, motor and mental speed), Similarities (abstract verbal reasoning), Arithmetic (mathematical problem solving), Matrix Reasoning (non-verbal abstract problem solving, inductive spatial reasoning), Digit span (attention, working memory, mental control), Information (general information acquired from culture, semantic memory). Intellectual functioning was evaluated with Information and Matrix reasoning subtests. An additional subtest, Letter-Number Sequencing was administered in schizophrenia patients, which along with 2 other primary subtests, Digit Span and Arithmetic, allowed the calculation of a Working Memory Index (WMI; auditory working memory and mental control).
- The CVLT was also used to evaluate verbal memory and executive functions(Delis et al. 2000)
- The Trail Making Test (TMT) for the executive functions as well as the speed of processing and visual attention evaluation (Reitan 1958); and verbal fluency for executive functions (Lezak et al. 2004).
- The Doors test (Baddeley et al. 1994) allowed a better assessment of memory.
- The Six elements test evaluates also executive functions.
- The Continuous Performance Test is a computerised measure of sustained, focussed attention or vigilance. The version used in the SZ cohort (CPT-IP) is a part of MCCB(Nuechterlein et al. 2008).

2.2.4. Environmental measures, learning disorders and comorbidities

- *Perinatal history* was recorded using medical childhood records when available and family information (birth weight, caesarean, prematurity and obstetrical complications).
- *Childhood adverse experiences* were evaluated with the Children Trauma Questionnaire, a 28-items self-report inventory that provides a valid screening for childhood maltreatment (Paquette et al. 2004).
- *Current and past addictions* (tobacco, alcohol, cannabis and other substances of abuse) were systematically recorded.
- *Learning and/or language disorders* were screened with Medical childhood records, as well as family information. The information was reported by 'yes/no' if at least one of the following disorders was found: dyslexia, dysorthographia, dyscalculia, dysphasia, dyspraxia, language delay, stuttering, delay in walking.
- *Common physical and biological parameters* were collected: peripheric inflammation (assessed with blood C-reactive protein (hs-CRP)>3mg/dL) and Body Mass Index (BMI).

2.3. Statistical analysis

Sociodemographics, clinical data, and ongoing medical treatments are presented as the mean (SD) for continuous variables and frequency distribution for categorical variables. Univariate associations between demographic, clinical characteristics, cognitive performances as well as psychotropic medication associated with lateralisation were determined using the χ^2 test for categorical variables, Student's *t*-test or Mann–Whitney test depending on the distribution for continuous variables. As more traditional levels (such as 0.05) can fail to identify variables known to be important, we chose a *p*-value cut-off point of 0.20 for the selection process of variables in a multivariate model with stepwise selection (Bendel and Afifi 1977; Mickey and Greenland 1989; Bursac et al. 2008).

Concerning cognitive analyses, a sensitivity analysis excluding individuals with current mood episodes (YMRS > 10 or Calgary > 6), a history of neurological/

sensory disorders, substances-related disorders in the past month, and electro-convulsive therapy in the past year, were performed. Bonferroni correction for multiple testing has been carried out.

This study was a confirmatory study. Analyses were conducted using SAS-9.3 (SAS Statistical Institute, Cary, North Carolina). All statistical tests were 2-tailed, with the α level set at 0.05.

3. Results

Overall, 667 individuals with SZ were recruited between January 2009 and January 2018. Table 1 presents the clinical and socio-demographic characteristics of the sample.

3.1. Clinical results

The prevalence of NRH and mixed-handedness were respectively 42.4% ($n = 283$) and 36.6% ($n = 244$).

- *Sociodemographic and clinical factors associated with NRH*
- In the univariate analysis, NRH was associated with a lower education level ($p = 0.031$; Table1). In the multivariable analyses, NRH was slightly associated with cannabis use disorder ($p = 0.045$). No association was found between NRH and perinatal factors, childhood trauma, clinical symptoms, neurological side effects, medication, obstetrical complications or elevated CRP.
- *Sociodemographic and clinical factors associated with mixed-handedness*
- In the *univariate* analysis, mixed-handedness was associated with general symptoms severity (PANSS general score, $p = 0.045$), current depressive episode ($p = 0.006$), higher level of childhood trauma (CTQ total score), current cannabis use ($p = 0.029$) and less akathisia ($p = 0.016$). In multivariable analyses, mixed-handedness was associated with positive symptoms ($p = 0.041$), current depressive episode ($p = 0.005$), current cannabis use disorder ($p = 0.024$) and less akathisia ($p = 0.019$). No association was found between mixed-handedness, obstetrical complications, medication or elevated CRP.

3.2. Cognitive results

We performed cognitive analyses in a sub-sample of 396 patients, excluding patients with potential confounding factors on cognitive performance regarding inclusion criteria (results are presented in Table 2). Mixed-handedness was associated with poorer performances at the Picture completion task ($p = 0.040$). After a Bonferroni correction, this association was no longer significant.

No association was found between NRH and any of the cognitive subtasks.

3.3. Learning and/or language disorders

Learning and language disorders were found in 9.59% ($n = 64$) out of the total sample (Table 3). Among them, dyslexia was the most frequent trouble (4.04%, $n = 27$).

3.3.1. Association between NRH and learning/language disorders

The two groups differ when comparing the presence/absence of at least one disorder, with NRH associated with the presence of a history of learning/language disorder (13.9%, $n = 35$, versus 8.4%, $n = 29$, $i = 0.032$).

3.3.2. Association between mixed-handedness and learning/language disorders

The two groups did not differ when comparing the presence of at least one learning/language disorder.

4. Discussion

The main finding is that NRH and mixed-handedness in schizophrenia are much higher than what is reported in the general population. This suggests that schizophrenia has an important neurodevelopmental origin, similar to what is seen in neurodevelopmental diseases. In this sample, learning and language disorders were also strongly associated with NRH, but not particularly with mixed-handedness. NRH was slightly associated with current cannabis use but not with other features. On the other hand, mixed-handedness was associated with positive symptoms (although weakly, $p = 0.045$), current depressive episode ($p = 0.020$), current cannabis disorder ($p = 0.044$) and less akathisia ($p = 0.009$), suggesting a specific clinical profile. Cognitive findings do not support a disadvantage for NRH or mixed-handedness participants, in line with the largest study to date until the present one (Deep-Soboslay et al. 2010). No association was found with trauma history, birth complications, peripheral inflammation or body mass index.

NRH prevalence is very high in this sample (42.4%) in comparison to previous studies (fluctuating around 25% (Dragovic and Hammond 2005)), but in line with

Table 1. Sociodemographic and clinical factors associated with lateralisation in a sample of 667 patients with schizophrenic disorders – Univariate and multivariate analysis.

	Mixed-handedness $n = 244$, 36.6	Non mixed-handedness $n = 423$, 63.4%	Univariate analysis p	Multivariate analysis Or_a (95% CI)	p^*	NRH $n = 283$, 42.4%	RH $n = 384$, 57.6%	Univariate analysis p	Multivariate analysis Or_a (95% CI)	p^*
Demographic characteristics										
Gender										
Male	191 (78.3)	313 (74.0)	0.2150			219(77.4)	285 (74.2)	0.3469		
Female	53 (21.7)	110 (26.0)				64 (22.6)	99 (25.8)			
Age (years), mean (SD)	**31.1 (9.2)**	**32.4 (9.3)**	**0.1057**			**31.2 (9.0)**	**32.4 (9.5)**	**0.0942**		
High education level (>high School), *n* (%)	**85 (37.1)**	**167 (44.7)**	**0.0687**			**97 (36.9)**	**155 (45.6)**	**0.0316**		
Disease characteristics										
Type of SZ										
Schizophrenia	190 (77.9)	318 (75.2)	0.6815			216 (76.3)	292 (76.0)	0.9192		
Schizo-affective disorders	51 (20.9)	97 (22.9)				63 (22.3)	85 (22.1)			
Schizophreniform disorders	3 (1.2)	8 (1.9)								
Duration of illness (years), mean (SD)	10.0 (7.5)	10.7 (8.1)	0.3777			10.2 (7.5)	10.6 (8.2)	0.4660		
Age of SZ onset (years), mean (SD)	21.2 (6.0)	21.7 (6.5)	0.5087			**21.0 (6.0)**	**21.9 (6.5)**	**0.1003**		
DUP, (years) mean (SD)	1.2 (2.5)	1.6 (3.4)	0.3130			1.4 (2.6)	1.5 (3.4)	0.9575		
Positive symptoms (PANSS positive score), mean (SD)	**15.3 (6.0)**	**14.3 (5.2)**	**0.1058**	**1.03 (1.00–1.07)**	**0.041**	**15.0 (5.8)**	**14.4 (5.3)**	**0.1894**		
Negative symptoms (PANSS negative score), mean (SD)	20.2 (6.9)	20.7 (7.4)	0.6118			20.2 (7.0)	20.8 (7.3)	0.2792		
General psychopathology (PANSS general score), mean (SD)	**36.6 (10.1)**	**34.8 (9.9)**	**0.0216**			**36.3 (10.3)**	**34.9 (9.8)**	**0.0842**		
Depressive episode (CDSS >6)	**70 (29.7)**	**82 (20.2)**	**0.0065**	**1.81(1.20–2.75)**	**0.005**	**75 (27.5)**	**77 (20.9)**	**0.0516**		
Manic symptoms (YMRS score), mean (SD)	2.2 (3.5)	2.2 (3.7)	0.6365			2.1 (3.4)	2.2 (3.8)	0.8565		
Global functioning (GAF), mean (SD)	**47.7 (11.6)**	**49.7 (13.3)**	**0.0596**			48.2 (12.1)	49.6 (13.2)	0.2018		
CTQ score total, mean (SD)	**42.9 (12.0)**	**41.4 (11.7)**	**0.0464**			**42.9(12.4)**	**41.3(11.4)**	**0.0787**		
Comorbidities										
Current daily tobacco smoking, *n* (%)	131 (55.5)	219 (55.0)	0.9058			153 (56.0)	197 (54.6)	0.7118		
Current Alcohol use disorder, *n* (%)	13 (5.3)	24 (5.7)	0.8509			16 (5.7)	21 (5.5)	0.9179		
Current cannabis use disorder, *n* (%)	**25 (10.3)**	**24 (5.7)**	**0.0293**	**2.12 (1.10–4.08)**	**0.024**	**27 (9.5)**	**22 (5.7)**	**0.0622**	**1.93 (1.01–3.70)**	**0.045**
Lifetime cannabis use, *n* (%)	75 (46.6)	124 (44.8)	0.7125			87 (47.3)	112 (44.1)	0.5083		
Body mass index, mean (SD)	26.0 (4.9)	26.2 (5.3)	0.9892			26.1 (5.0)	26.1 (5.3)	0.8810		
Abnormal CRP (>3)	37 (23.3)	72 (26.8)	0.4225			130 (65.3)	164 (61.0)	0.3346		
Treatments										
CPZ eq (mg/day)	547.4 (478.1)	617.4 (536.5)	0.3355			556.9 (597.1)	611.1 (576.2)	0.5736		
First Generation Antipsychotic, *n* (%)	55 (27.4)	83 (24.3)	0.4239			61 (26.3)	77 (24.8)	0.6846		
Second generation antipsychotic, *n* (%)	181 (90.1)	314 (91.8)	0.4847			208 (89.7)	287 (92.3)	0.2859		
Antidepressant, n (%)	69 (34.2)	110 (32.2)	0.6324			81 (34.8)	98 (31.5)	0.4243		
Mood stabiliser, *n* (%)	39 (19.4)	61 (17.8)	0.6493			43 (18.5)	57 (18.3)	0.9510		
Neurological side effects										
Akathisia, *n* (%)	**27 (11.7)**	**75 (19.1)**	**0.0159**	**0.53 (0.31–0.90)**	**0.019**	38 (14.1)	64 (18.0)	0.1918		
Parkinsonism, *n* (%)	**33 (15.0)**	**42 (11.1)**	**0.1661**			**42 (11.1)**	**33 (15.0)**	**0.1661**		
Tardive dyskinesia, *n* (%)	19 (8.2)	32 (9.1)	0.6812			22 (8.2)	33 (9.2)	0.6311		
Perinatal factor (at least one), *n* (%)	46 (18.9)	80 (18.9)	0.9848			54 (19.1)	72 (18.8)	0.9140		
Birth weight (g), mean (SD)	3280.9 (542)	3275.9 (584)	0.8782			3282.7 (520)	3274 (601)	0.8782		
Obstetrical complications, *n* (%)	9 (13.8)	15 (15.2)	0.8170			13 (16.9)	11 (12.6)	0.4433		
Caesarean, *n* (%)	30 (14.1)	45 (12.3)	0.5363			33 (13.3)	42 (12.7)	0.8520		
Prematurity, *n* (%)	17 (7.0)	29 (6.9)	0.9564			23 (8.1)	23 (6.9)	0.2816		

Note. Statistically significant values are in bold ($p < 0.05$). NRH, Non-right-handedness; RH, Right-Handedness; SD, standard deviation; DUP, duration of untreated psychosis; PANSS, Positive and Negative Syndrome Scale; YMRS, Young Mania rating Scale; CDSS, Calgary Depression rating Scale for Schizophrenia; GAF, Global assessment of Functioning; CTQ, Children Trauma Questionnaire.
*Multivariate logistic regression model with all variables with p-value <0.20.

Table 2. Cognition associated with lateralisation in a sample of 396 patients with schizophrenia (SZ) – univariate analyses.

	Mixed-handedness $n = 135$, 34.1%	Non mixed-handedness $n = 261$, 65.9%	p	NRH $n = 283$, 42.4%	RH $n = 384$, 57.6%	p
Premorbid intellectual ability						
fNART based premorbid IQ, mean (SD)	104.8 (8.2)	103.4 (8.7)	0.1550	104.5 (8.3)	104.0 (8.6)	0.5116
Working memory						
Digit span (standard score), mean (SD)	8.1 (2.6)	7.9 (2.6)	0.6119	8.1 (2.9)	8.1 (2.8)	0.8712
Letter-Number Sequencing (Standard score), mean (SD)	7.8 (2.3)	8.0 (2.8)	0.5591	9.4 (2.7)	9.7 (2.9)	0.2500
Arithmetic (standard score), mean (SD)	10.3 (5.2)	9.9 (5.1)	0.3780	9.7 (5.1)	10.1 (5.3)	0.3122
Working Memory Index (WMI), mean (SD)	87.2 (12.7)	86.1 (14.6)	0.4805	86.0 (14.2)	86.8 (15.5)	0.4919
Learning abilities, episodic and semantic memory						
CVLT short delay free recall, raw score, mean (SD)	9.6 (3.4)	9.5 (3.6)	0.8210	9.3 (3.4)	9.5 (3.6)	0.4550
CVLT long delay free recall, raw score, mean (SD)	10.1 (3.3)	10.0 (3.6)	0.8273	9.7 (3.4)	9.9 (3.5)	0.3546
CVLT recognition, raw score, mean (SD)	14.4 (1.9)	14.6 (3.2)	0.8332	14.4 (2.0)	14.6 (2.8)	0.7286
Doors test (A&B) (total), mean (SD)	15.7 (4.1)	15.6 (4.2)	0.9533	15.6 (4.2)	15.8 (4.3)	0.5861
Information (Standard score), mean (SD)	8.9 (3.1)	8.8 (3.1)	0.7771	9.1 (3.0)	9.0 (3.2)	0.7427
Executive functions and problem solving						
Trail Making Test B (time in s)	102.5 (65.2)	101.7 (52.8)	0.2733	105.4(64.8)	104.5 (57.6)	0.4876
Trail Making Test B-A (time in s)	62.9 (53.3)	60.3 (43.3)	0.6746	64.7(53.6)	62.2 (46.8)	0.9159
Trail Making Test B-A (errors)	0.62 (2.1)	0.52 (1.3)	0.6818	0.67 (1.8)	0.48 (2.3)	0.2689
CVLT intrusions, raw score, mean (SD)	5.08 (7.1)	4.61 (5.6)	0.7845	5.4 (6.7)	5.3 (6.1)	0.7208
CVLT perseverations, raw score, mean (SD)	6.4 (7.2)	5.5 (5.5)	0.3391	6.2 (6.6)	5.4 (5.4)	0.1960
Verbal fluency, breaking rules, raw score, mean (SD)	0.49 (1.1)	0.38 (1.2)	0.4305	0.47 (1.0)	0.47 (1.1)	0.8624
Verbal fluency, perseverations, raw score, mean (SD)	0.37 (0.8)	0.60 (1.7)	0.1814	0.42 (0.8)	0.61 (2.2)	0.5731
Verbal fluency (total correct), mean (SD)	17.9 (6.6)	18.6 (6.7)	0.4081	18.1 (6.4)	18.8 (7.0)	0.1724
Similarities (standard score), mean (SD)	9.2 (3.6)	9.1 (3.3)	0.5098	9.2 (3.3)	9.1 (3.2)	0.6065
Matrix reasoning (standard score), mean (SD)	16.8 (5.6)	17.1 (5.3)	0.8118	16.9 (5.4)	17.1 (5.2)	0.5778
6 elements test (errors), mean (SD)	7.7 (5.2)	7.4 (4.9)	0.6566	805.2 (231.8)	811.8 (232.4)	0.6031
6 elements test (total score), mean (SD)	805.4 (217.4)	822.1 (222.7)	0.3473	7.6 (5.3)	7.4 (5.0)	0.6808
Visual attention and speed of processing						
Trail Making Test A (time in s), mean (SD)	41.0 (24.0)	41.8 (17.1)	0.1235	42.1 (24.0)	42.5 (17.9)	0.1118
Digit-Symbol Coding (standard score), mean (SD)	5.9 (2.7)	6.3 (3.2)	0.5489	6.0 (2.7)	6.1 (3.1)	0.7634
Picture completion (total score), mean(SD)	15.0 (5.2)	16.0 (5.6)	**0.0404***	15.6 (5.6)	16.1 (5.5)	0.2408
CPT-IP d-prime, mean (SD)	2.4 (0.6)	2.4 (0.7)	0.6499	1.9 (0.7)	1.9 (0.7)	0.8493

Note: Statistically significant values are in bold ($p < 0.05$). NRH, Non-right-handedness; RH, Right-handedness; SD, standard deviation; fNART, French National Adult Reading Test; CVLT, California Verbal Learning Test; CPT-IP, Continuous Performance Test-Identical Pairs.
Individuals with major depressive episode, neurological/sensory disorders, and those with substances-related disorders in the past month and electro-convulsive therapy in the past year were excluded from the analysis.
*Non significant after Bonferroni correction

Table 3. Learning/language disorders associated with lateralisation in a sample of 667 patients with schizophrenia (SZ) – univariate analyses.

	Mixed-handedness $n = 244$, 36.6	Non mixed-handedness $n = 423$, 63.4%	p	NRH $n = 283$, 42.4%	RH $n = 384$, 57.6%	p
History of learning/language disorder						
At least one, *n* (%)	27 (12.4)	37 (9.7)	0.3133	35 (13.9)	29 (8.4)	**0.0325**
Disgraphia, *n* (%)	2 (0.9)	0	0.1325	2 (0.8)	0	0.1786
Dyslexia, *n* (%)	10 (4.6)	17 (4.5)	0.9487	15 (5.9)	12 (3.5)	0.1539
Dysphasia, *n* (%)	0	1 (0.3)	1.0000	0	1 (0.3)	1.0000
Dyspraxia, *n* (%)	1 (0.5)	0	0.3645	1 (0.4)	0	0.4231

Note. Statistically significant in bold ($p < 0.05$). NRH, Non-right-handedness; RH, Right-Handedness.

a comparable out-patients study on a small sample (Webb et al. 2013). Earlier studies may have underestimated NRH in SZ, due to cultural influences on hand preference, including the negative stigma associated with left-handedness, whereas our sample is relatively young and is probably less affected by fear of this stigma. Contrary to what has been suggested by Deep-Soboslay et al., the higher prevalence of NRH and mixed-handedness in schizophrenia can not be fully explained by enrichment of previously studied samples with patients having childhood neurodevelopmental problems. When examining the prevalence in our sample after exclusion of individuals with a history of learning/language disorders, we still find a high prevalence of NRH and mixed-handedness (41.2% and 36.1%, respectively).

More specifically, mixed-handedness prevalence is found in one patient in three (36.6%), with specific unexpected features, as less akathisia, current depressive disorder, high positive symptoms or more cannabis use disorder. Given that medication remained unchanged at least during the last 4 weeks, the prevalence of akathisia reported here reflects chronic akathisia and not recent onset or withdrawal akathisia.

Importantly, the two groups were comparable concerning medication (CPZ equivalents, proportion of first and second-generation antipsychotics, antidepressant and mood stabiliser). We did not replicate earlier findings of more tardive dyskinesia in NRH patients (McCreadie et al. 1982). To our knowledge, this study is the first to investigate current mood disorders in mixed-handed individuals with SZ, and it has never been explored in non-clinical populations, making it difficult for any comparison. The current depressive disorder may be a specific feature, possibly reflecting lateralised dysfunction of frontal lobes, as a depressive disorder may be linked to anomalies of activation of the left versus right frontal lobe (Foster et al. 2011). This association may also reflect undiagnosed depressive disorder in mixed-handed patients, for an unknown reason making them more difficult to evaluate in current practice (they do not differ for the rate of antidepressant treatment). Moreover, patients with mixed-handedness also presented more positive symptoms, although the association is weak. These results reinforce the assumption that mixed-handedness is linked to psychosis-proneness, as reported in a large body of literature on the topic in non-clinical samples (Chapman and Chapman 1987; Kim et al. 1992; Poreh 1994; Richardson 1994; Claridge et al. 1998, 1998; Shaw et al. 2001; Gregory et al. 2003; Dragovic et al. 2005; Annett and Moran 2006; Schürhoff et al. 2008; Chapman et al. 2011; Barrantes-Vidal et al. 2013).

Finally, cannabis use disorder was slightly associated with NRH, and more strongly with mixed-handedness. It is well-recognized that cannabis use disorder is associated with worse clinical course and functioning in schizophrenia (Mallet et al. 2017) and may also reflect an undiagnosed attention deficit hyperactivity disorder (ADHD) (Wallace et al. 2019). Individuals with mixed-handedness could also share neurodevelopmental patterns with ADHD subjects, as cannabis is thought to alleviate their cognitive disorders (Anker et al. 2020). Yet to date, no existing studies provide sufficient, high-quality data to suggest that cannabis should be recommended for the treatment of autism spectrum disorders or ADHD (Hadland et al. 2015). In line with the present results, a prospective study on a pregnancy–offspring cohort suggested that mixed-handedness could be a marker of both severities of prenatal exposure to maternal distress and of increased risk of ADHD symptoms in childhood (Rodriguez and Waldenström 2008). If we consider that cannabis use is a marker of undiagnosed ADHD in the mixed-handedness group, further studies are definitely needed to explore the links between schizophrenia, ADHD and mixed-handedness. An alternative (but not exclusive) hypothesis is that cannabis may alleviate akathisia in these subjects, explaining the lower prevalence of this medication's side effects. Cannabis compounds act through basal ganglia, are known to leverage involuntary movements and have been shown to induce restlessness in non-SZ individuals (Juncal-Ruiz et al. 2017). In a relatively small sample (groups around 35 subjects) (Zhornitsky et al. 2010), cannabis was associated with extrapyramidal symptoms (and akathisia) in non-schizophrenia individuals with comorbid substance use disorder, but not in patients with a dual diagnosis of SZ and cannabis use disorder. Some components of cannabis could have a pharmacological action against akathisia in patients, as it has been reported against dyskinesia (Niehaus et al. 2008). It is known that SZ individuals present specificities of the endocannabinoid system, and exogenous cannabis may have a specific action against this medication side effect, particularly when they present a particular neurodevelopmental trajectory (represented here by mixed-handedness). Thus, in this subgroup with a stronger neurodevelopmental pattern (weak brain laterality), we hypothesise that cannabis use disorder could be an attempt to alleviate depressive symptoms, cognitive deficits and neurological side effects.

We found no association between NRH or mixed-handedness and peripheral inflammation or perinatal factors (including birth weight) after accounting for important confounders. Taken as a whole, our results do not support the hypothesis that atypical handedness is associated with developing SZ through inflammatory or other perinatal impacts on neurodevelopment or via other materno-fetal pathways. However, there may potentially be shared genetic architecture for NRH or mixed-handedness and SZ, potentially by uncommon and different mechanisms, as suggested recently (Wang Q et al. 2018; Abdolmaleky et al. 2019). In a review and meta-analysis of structural MRI, authors postulate that laterality interacts with sex across the schizophrenia/bipolarity continuum, and show common and distinct features in lateralisation in both disorders (Crow et al. 2013). While the influence of male hormones on brain lateralisation is well known, our data do not support a sexual dimorphism for NRH in SZ.

To the best of our knowledge, this study is the first to demonstrate the link between NRH (but not mixed-handedness) and learning and language disorders in SZ. Data on handedness and developmental or learning/language disorders remain scarce to date. Yet,

recent data converge towards a common early genetic and neurodevelopmental mechanism underlying dyslexia and handedness (Brandler and Paracchini 2014). Further studies are needed to investigate properly the links between NRH, all learning disorders and schizophrenia.

Finally, our data do not support a link between NRH (including mixed-handedness) and a frankly poorer neurocognition in SZ. Given the size of this cohort and the high rates of NRH and mixed-handedness, it is unlikely that we failed to find a strong association between handedness and SZ because of a lack of adequate statistical power. Given the high prevalence of learning disorders associated with NRH and mixed-handedness, these patients could have acquired different compensation mechanisms via neuroplasticity phenomena, involving appropriate rehabilitations. Taken together, these results are consistent with the literature on handedness and cognition in non-psychiatric samples, showing a slight but inconsistent disadvantage for NRH (Sommer et al. 2001; Bishop 2013), and with the latest and largest study ($n = 375$) on cognitive correlates of NRH in SZ, that did not find supporting evidence of a relevant association (Deep-Soboslay et al. 2010).

4.1. Perspectives

Longitudinal studies are required to confirm a temporal relationship between NRH/mixed-handedness and (i) SZ (studies on the risk of psychotic transition are required); (ii) learning/language disorders in SZ; (iii) ADHD in SZ. Finally, it would be interesting to evaluate the disease progression of NRH patients, as NRH has emerged as one potential marker of selective vulnerability in degenerative diseases (Botha et al. 2018).

4.2. Strengths and limitations

First, this study is cross-sectional; therefore we were not able to investigate the direction of effect between NRH (and mixed-handedness) and SZ, symptoms, cognition, or learning/language disorders. Longitudinal studies would be valuable to investigate the temporal relationship between these factors. Second, it should be pointed out that handedness is only one marker of lateralisation and the finding of an excess of NRH and mixed-handedness in SZ, however robust it is, only suggests that brain lateralisation and schizophrenia are linked. The literature on evidence for abnormalities in structural or functional hemispheric asymmetries is poorer and less consistent than the excess of NRH. Recently, however, several teams provided an overview of neuroimaging findings that, taken together, suggest anomalous lateralisation in SZ also manifests in the brain (Crow et al. 2013; Hirnstein and Hugdahl 2014; Wang Q et al. 2018; Abdolmaleky et al. 2019).

The main strengths of this study include the use of homogenous and exhaustive standardised protocols and neuropsychological assessment in a large national multicentric study, which provides a 'real-world' patient sample. This study is the largest to explore clinical and cognitive correlates of NRH and mixed-handedness in SZ to date. Important confounding factors were taken into account for the first time, especially socio-demographic characteristics, substance abuse disorders, neurological disorders, perinatal factors and medication. Our samples were relatively young (with a mean age under 40). The use of a gold-standard questionnaire to provide handedness is also clearly an advantage over previous studies.

5. Conclusions

Our data strongly supports the view that there is a link between handedness, brain lateralisation and schizophrenia. NRH and mixed-handedness are common in patients with SZ, and may reflect a neurodevelopmental burden in these patients. NRH was associated with more cannabis use disorder and with learning and language disorders, rising further research perspectives. Mixed-handedness was associated with positive symptoms, current depressive episode, current cannabis use disorder and less akathisia, suggesting a specific subgroup and a more severe profile. However, our results did not confirm greater cognitive impairment in these patients.

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Author contributions

All authors acquired the data, which J. Mallet, O. Godin, G. Fond, Y. Le Strat and C. Dubertret analysed. O. Godin completed the statistical analyses. J. Mallet wrote the article, which all authors reviewed. All authors approved the final version to be published.

Disclosure statement

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