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Title: Executive functions in schizophrenia aging: differential effects of age within specific executive functions

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Abstract

There are common cognitive and brain abnormalities in schizophrenia and healthy aging which may cumulate in schizophrenia aging. However, the course of executive deficits in late-life schizophrenia is still controversial as it remains unclear whether schizophrenia patients show accelerated aging. The use of specific models of executive functions might help to shed new lights on this issue. The aim of this study was then to determine how each of the four specific executive functions (shifting, updating, inhibition and access to long-term memory) is affected by aging in schizophrenia compared to healthy aging.

20 younger (age 18-34), 17 middle-aged (age 35-49) and 25 older (age 59-76) schizophrenia patients and 62 healthy comparison participants matched for gender, age and education performed a neurocognitive battery evaluating the four specific executive functions.

Schizophrenia patients performed worse than comparison participants on shifting, updating and access, whereas inhibition appeared preserved. Age affected the four functions with increased degradation of shifting and access in schizophrenia patients, whereas updating and inhibition showed a normal decline with age.

These results suggest a vulnerability of prefrontal and cingulate cortexes in schizophrenia aging. Moreover, as age affected the specific executive functions differently, remediation programs should be adapted to older patients. Models of specific executive functions are useful for understanding the complexity of cognition in schizophrenia and its course during later life so that healthcare can be adapted accordingly.

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Key Words: Schizophrenia; Adulthood; Aging; Executive functions; Miyake's model.

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1. Introduction:

Cognitive impairment is a core feature of schizophrenia and affects most of the cognitive domains (Heinrichs & Zakzanis, 1998; Mesholam-Gately, Giuliano, Goff, Faraone, & Seidman, 2009). Among those, executive functioning deals with problems of control and coordination which may emerge when the separate processes must work together (Logan, 1985). They are implicated in adapting behavior to diverse situations, creating a plan, initiating its execution, and persevering until its completion, and they mediate our ability to organize our thoughts in a goal-directed way (Jurado & Rosselli, 2007). Schizophrenia is the clinical pathology where the largest executive functions deficits are found (Snyder, Miyake, & Hankin, 2015). Since executive functions affect performance in a wide variety of cognitive variables (Kerns, Nuechterlein, Braver, & Barch, 2008; Salthouse, Atkinson, & Berish, 2003), their impairment would underlie other cognitive impairments in schizophrenia (Nathaniel-James, Brown, & Ron, 1996). It is therefore of a particular interest to focus on these functions in schizophrenia to adapt remediation programs accurately.

Moreover, recent findings suggest that schizophrenia is a neurodevelopmental disorder with cognitive impairments exhibited prior to the onset of the pathology (Meier et al., 2014; Sheffield, Karcher, & Barch, 2018). Cortical dysfunctions are observed during executive tasks including reduced activations in the prefrontal cortex, anterior cingulate cortex and thalamus (Minzenberg, Laird, Thelen, Carter, & Glahn, 2009). Recent studies also observed structural deterioration of white matter in networks involving the prefrontal cortex (Orellana & Slachevsky, 2013; Wagner et al., 2015). Thus, despite the heterogeneity of the findings concerning cortical dysfunctions in schizophrenia, impairment in prefrontal functioning, which is historically linked to executive functioning (Luria, 1966; Shallice, 1982), is consistently observed.

Executive functions are composed of multiple sub-functions which may be grouped together in three specific functions that are independent of each other but also correlated to the general concept of executive functioning (Miyake et al., 2000). These three functions are the ability to shift back and

80 forth between multiple tasks, operations or mental sets (shifting), the ability to include relevant new
81 information in working memory and suppress irrelevant information (updating), and the ability to
82 cancel prepotent but irrelevant behavior (inhibition). Based on this model, it has been shown that
83 these three specific functions are impaired in cognitive aging (Adrover-Roig, Sesé, Barceló, &
84 Palmer, 2012) and that their study helps describe the relations between age and cognitive functions
85 more accurately. Indeed, updating and inhibition mediated performance in autobiographical
86 memory (Piolino et al., 2010), whereas inhibition and shifting were involved in prospective memory
87 performance (Schnitzspahn, Stahl, Zeintl, Kaller, & Kliegel, 2013). Although this model is the most
88 commonly used, the authors acknowledge that it is not comprehensive and other factors may be
89 added (N. P. Friedman & Miyake, 2017). Accordingly, Some authors (Fisk & Sharp, 2004) extended
90 Miyake et al.'s work and found a fourth specific executive function, labeled "access", which reflects
91 the efficiency of access to long-term memory. The authors observed that access was the only specific
92 executive function not affected by age.

93 Models showing multiple independent executive processes are of interest to explain cognitive
94 heterogeneity in schizophrenia (Reichenberg & Harvey, 2007). Thus, several experiments used tests
95 that measure these specific functions in schizophrenia and found deficits in shifting (Ceaser et al.,
96 2008; Tyson, Laws, Roberts, & Mortimer, 2004), updating (Culbreth, Westbrook, & Barch, 2016;
97 Zanelli et al., 2010), inhibition (Laurenson et al., 2015; Westerhausen, Kompus, & Hugdahl, 2011)
98 and access (Rossell, 2006; Szöke et al., 2005). However, only a few studies about schizophrenia
99 included at least the three functions described by Miyake *et al.* (2000). Some studies (Chan, Chen,
100 & Law, 2006; Donohoe, Corvin, & Robertson, 2006; Wongupparaj, Kumari, & Morris, 2015) found
101 significant differences between patients and comparison participants with respect to measures of the
102 three functions. Another study (Raffard & Bayard, 2012) also found group differences with each
103 specific function and their results revealed greater heterogeneity in schizophrenia than in controls.
104 Some patients presented no deficits, some had deficits on all measures, and others were impaired

only with regard to one or two specific executive functions. Furthermore, one study (Rabanea-Souza et al., 2016) found that impaired shifting and updating appear to be predictors of schizophrenia diagnosis, whereas preservation of inhibition and updating seem to be predictors of symptom remission. Thus, this research points to the usefulness of assessing specific executive functions to understand executive functioning in schizophrenia. However, to the best of our knowledge, no study has explored specific executive functions in older schizophrenia patients, despite specific executive functions being a good indicator of cognitive performance among normal aging. In fact, reduced executive performance in healthy older participants (Andrés & Van der Linden, 2000) is a predictor of the impairment of other processes such as verbal memory (Bryan, Luszcz, & Pointer, 1999; Taconnat et al., 2009). Although it seems executive functions alone do not account for all age-related deficits (Cona, Arcara, Amodio, Schiff, & Bisiacchi, 2013; Verhaeghen & Cerella, 2002), it would seem they are particularly implicated in the most difficult tasks where older participants show a drop in performance (Cona et al., 2013; Silver, Goodman, Gur, Gur, & Bilker, 2011; Verhaeghen & Cerella, 2002).

The cognitive deficits appeared even before the onset of schizophrenia (Meier et al., 2014; Sheffield et al., 2018), and its decline in late life is strongly linked to functional competences (Harvey, Parrella, White, Mohs, & Davis, 1999; Kalache et al., 2015). Yet, despite the growing number of older patients with schizophrenia (C. Cohen et al., 2008; Lee et al., 2018), their course during late adulthood remains unclear because of the lack of studies investigating this issue (Herold, Schmid, Lässer, Seidl, & Schröder, 2017; Rajji & Mulsant, 2008) and because normal aging is also associated with executive decline (Cona et al., 2013; Silver et al., 2011; Verhaeghen & Cerella, 2002). Moreover, cognitive changes during healthy aging are “surprisingly similar to the changes that are seen in people with schizophrenia” (Harvey & Rosenthal, 2018). This similarity also involve brain anatomy because grey and white matter atrophy in prefrontal regions are reported in both healthy aging (Teipel et al., 2010) and schizophrenia (Orellana & Slachevsky, 2013; Zierhut et al., 2013). It

is therefore possible that aging has more deleterious effects in schizophrenia patients than in healthy people. Thus, it is of special interest to ascertain whether cognitive deficits in schizophrenia patients increase more with aging than is the case with healthy participants. This knowledge is necessary to adapt treatments and cognitive remediation programs for older patients. Schizophrenia patients show accelerated physical aging (Jeste, Wolkowitz, & Palmer, 2011), including for their brain (Schnack et al., 2016; Sheffield et al., 2016) compared to healthy controls of the same age. Studies are less consistent, however, concerning neurocognition which is linked to adaptive functioning (Green, 2016; Harvey et al., 1999), quality of life (Mohamed et al., 2008), and social and everyday living skills (Evans et al., 2003; Kalache et al., 2015; McClure et al., 2007). Some authors observed accelerated aging only with executive functions (Fucetola et al., 2000; Herold et al., 2017), whereas others indicated that it did not affect executive functions at all, but processing speed and verbal learning (Loewenstein, Czaja, Bowie, & Harvey, 2012), or visuo-spatial functions (Stirling et al., 2003) instead. The results of a meta-analysis failed to report accelerated aging (Irani, Kalkstein, Moberg, & Moberg, 2011) on several functions, including executive functions, and the authors of another study even observed a normalization of cognition with aging in schizophrenia patients (Irani et al., 2012). Several factors may account for these controversial results, including the kind of tasks used to measure cognition, whether or not patients are institutionalized (Bowie, Reichenberg, McClure, Leung, & Harvey, 2008), task difficulty (Knapp, Viechtbauer, Leonhart, Nitschke, & Kaller, 2017) and, more critically, the age of the older patients included in the study (J. I. Friedman et al., 2001; Rajji & Mulsant, 2008).

We aimed to determine whether a particular specific executive function could be a sensitive indicator of accelerated aging in schizophrenia. Based on previous studies, we hypothesized that patients' performance would be lower in all four executive functions (shifting, updating, inhibition and access), and that younger participants would perform better than older participants in all executive functions except for "access". Finally, we surmised that depending on the specific

executive function considered, aging would show differential effects between schizophrenia patients and comparison participants. More precisely, according to previous studies showing accelerated aging in tasks assessing shifting (Fucetola et al., 2000; Herold et al., 2017), we hypothesized that accelerated aging would occur at least in this specific function. However, concerning the other specific functions, due to the lack of data in the literature about cognitive aging in schizophrenia we cannot postulate precise hypotheses.

2. Methods and material

2.1. Participants

We report how we determined our sample size, all data exclusions (if any), all data inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, all manipulations, and all measures in the study. This study was conducted in accordance with ethical standards and had the approval of the local ethics committees (EudraCT 2010-A00857-32 and PRI 2000, HUS N°2326). Before the investigation started, all the participants provided written informed consent after receiving a full explanation about the study. The participants were 62 clinically-stable outpatients with schizophrenia recruited from the Psychiatric Department of the University Hospital. The following inclusion/exclusion criteria were established prior to data analysis, and all manipulations and measurements performed in the study. According to the consensus opinion of their current psychiatrist and a senior psychiatrist on the research team, all of the patients met the criteria for schizophrenia as set out in the Diagnostic and Statistical Manual of Mental Disorders -IV-TR. Patients with any current co-morbid neurologic or psychiatric disorder, including alcohol or substance abuse or dependence, were not included. Their psychiatric symptoms were assessed according to the Positive And Negative Symptoms Scale (PANSS) (Kay, Fiszbein, & Opler, 1987). Anxiety and depression were screened using the Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983). Verbal intelligence quotient (IQ) was evaluated using

vocabulary and arithmetic tests taken from the short version of the Wechsler Adult Intelligence Scale, revised (WAIS-R) (Silverstein, 1982). Patients received stable doses of psychotropic medication for at least 4 weeks. In addition, 62 healthy comparison participants who matched the patients in terms of age, gender and education as recommended (Fioravanti, Bianchi, & Cinti, 2012), were recruited from the community. None of these participants had a known neurological or psychiatric affection or was currently suffering or had suffered in the past from alcohol or substance abuse or dependence. The participants were divided into three age groups: Young participants were under 35, middle-aged participants were between 35 and 49, and older participant were over 59. These age groups were chosen according to previous research (Fucetola et al., 2000) with the aim of increasing the age of older participants. In order to more clearly distinguish the effect of age, participants between the ages of 50 and 59 were not recruited. Our sample size was based on a power analysis showing that 124 participants allow 85% power for detecting an effect size of .3 with an alpha of .05. These criteria go beyond those of a recently published study (Facchin, Sartori, Luisetti, De Galeazzi, & Beschin, 2019). Table 1 presents the demographical, clinical and descriptive statistics of the group comparison data.

Table 1. Demographic characteristics of patients with schizophrenia and comparison participants by age group (standard deviations shown in brackets).

	Schizophrenia patients			Healthy comparison participants		
	Young n=20	Middle aged n=17	Older n=25	Young n=20	Middle aged n=17	Older n=25
Men/women	13/7	7/10	15/10	13/7	7/10	15/10
Age (years) ^b	28.3 (4.3)	42.8 (4.4)	63.4 (4.0)	28.9 (4.3)	42.7 (4.0)	63.7 (3.9)
Education level	11.0 (1.4)	12.2 (3.2)	11.0 (3.6)	11.6 (1.2)	12.1 (2.9)	10.9 (3.3)
PANSS total	65.8 (19.8)	72.5 (19.8)	64.0 (16.9)			
PANSS Positive score	15.4 (4.3)	14.4 (4.6)	13.6 (6.0)			
PANSS Negative score	17.5 (6.9)	20.6 (9.0)	18.2 (6.2)			

PANSS General psychopathology	32.9 (10.9)	37.4 (9.3)	32.3 (7.9)			
HADS Anxiety ^{a, b}	9.5 (4.0)	7.7 (3.9)	6.6 (3.0)	5.3 (2.2)	7.0 (4.7)	5.0 (2.8)
HADS Depression ^{a, b}	6.2 (3.0)	7.7 (3.9)	5.6 (2.9)	4.1 (3.0)	4.6 (3.4)	3.0 (2.2)
Verbal IQ ^{a, b}	83.2 (18.5)	85.9 (16.3)	89.8 (12.1)	90.7 (14.8)	94.8 (11.9)	108.9 (12.9)

Notes. PANSS= Positive And Negative Symptom Scale; HADS= Hospital Anxiety and Depression Scale; IQ= Intelligence Quotient.

^a significant group difference between patients and comparison participants

^b significant age difference

2.2. Material

Neuropsychological tests were selected according to the framework devised by Miyake *et al* (Miyake et al., 2000) which distinguishes three specific executive functions (shifting, updating and inhibition) with the addition of the efficiency of access to long-term memory (Fisk & Sharp, 2004). Two tests were used for each specific function. No part of the study procedures was pre-registered prior to the research being conducted. Computerized tasks used in this article (Number-letter task and Self-Ordered Pointing Task) are available at: <https://osf.io/2w34k/>

The scores used in the analyses consisted of:

2.2.1 Shifting tasks:

Plus-minus task (Jersild, 1927; Spector & Biederman, 1976): This task consisted of three lists of two digit numbers. Participants were instructed to add 3 to all the numbers in the first list and to write down the result, to subtract 3 in the second list and, finally, to alternate between adding and subtracting 3 in the third list. The shift cost was calculated as the difference between the time taken to complete the third list and the average of the time taken for the first and second lists: $T3 - [(T2 + T1) / 2]$ (Miyake et al., 2000).

Number-letter task (Rogers & Monsell, 1995): This task was computerized. A number-letter pair was presented in one of four quadrants on the screen. Participants were instructed to indicate whether the number was odd or even when the pair was presented in one of the upper quadrants,

and whether the letter was a consonant or a vowel when the pair was presented in either of the bottom two quadrants. The pairs were all presented in the upper quadrants for the first block of 32 items, in the bottom two quadrants for the second block and randomly in any of the quadrants in the last block of 32 items. The shift cost was calculated in the same way as in the plus-minus test: $T3 - [(T2 + T1) / 2]$ (Miyake et al., 2000).

2.2.2. Access tasks:

Verbal fluency: Two verbal fluency tasks were assessed, phonemic fluency (Letter P) and semantic fluency (category “animals”). The score was the number of correct words within 60 seconds.

2.2.3. Updating tasks:

N-back task (Clarys, Bugaiska, Tapia, & Baudouin, 2009; Perrotin, Belleville, & Isingrini, 2007): A list of 30 letters was read out to the participants, who were instructed to say aloud (yes/no) whether the current letter was the same as one of the three previous letters. To simplify the instructions for the older patients, participants were asked to compare the current letter not with one letter occurring earlier in the sequence but with the 3 previous letters. The next letter was read after the participant’s response. The score was the number of correct answers (hits and correct rejections). As there was no 0-back control condition, working memory performance cannot be separated from lower order functions.

Self-Ordered Pointing Task (Petrides & Milner, 1982): This computerized task consisted of 16 drawings presented together 16 times but each time with a different organization. Participants were instructed to choose a different drawing in each presentation, the aim being to select each of the 16 drawings during the 16 presentations. The score was the number of different drawings selected.

2.2.4. Inhibition tasks:

Stroop color word task (SCWT) (Stroop, 1935), card version: Two subtests of the SCWT were used. In the color naming baseline condition, participants were instructed to name the color of crosses (XXXX) within 45 seconds, and in the color-word condition, they had to name the color of the ink of words denoting a color within 45 seconds. Items were presented on a sheet of paper. To reduce the potential bias of patients' cognitive slowing, we used the following interference score (Li & Bosman, 1996): (Baseline – color word)/Baseline.

Hayling sentence Completion Test (HSCT) (Burgess & Shallice, 1996): In part A, participants were instructed to complete orally 15 sentences read by the experimenter by providing the appropriate final word. In part B, they had to complete 15 new sentences with a word that had no semantic link with the sentence. The scores were the time taken to complete part B and the number of errors in part B.

2.3. Data analyses

Data used in this article are available at: <https://osf.io/2w34k/>

Not all participants completed all the tests: 5 (4%) didn't complete the plus minus test (3 young patients, 1 middle-aged patient and 1 older patient), 1 (0.8%) the n-back test (1 older patient) and 10 (8%) the HSCT (1 young patient, 1 middle-aged patient, 6 older patients and 2 older comparison subjects). The missing data were replaced using Multiple Imputation by Chained Equations (MICE)¹.

In order to test the effects of Age (young, middle or old) and Group (healthy comparison participants vs. schizophrenia patients) and the interaction between Age and Group on executive functions, we

¹ MICE is a very flexible procedure with several advantages over other missing data approaches (Azur, Stuart, Frangakis, & Leaf, 2011). As MICE operates according to the assumption that missing data are missing at random, we tested our dataset with Little's Missing Completely At Random (MCAR) test. The result ($\chi^2 = 27.58$; $df = 21$; $p = .153$) indicates that the null hypothesis that data are missing completely at random cannot be dismissed. We therefore created 40 imputed datasets as recommended (Azur et al., 2011), and the means of these datasets were used to replace missing data. Statistical analyses were also run without replacing missing data and yielded the same results.

computed Z-scores for each task and then calculated the means between the two tests within each of the four executive domains (shifting, updating, inhibition and access) to create a composite index for these cognitive abilities². We then ran separate Analyses Of Variance (ANOVAs) on each index with Group and Age as independent variable. Tukey's test was used as a post-hoc test when age effects were observed.

Tukey's test was used as a post-hoc test when age effects were observed.

All analyses were run on SPSS Statistics 23 (IBM Corp, 2015), with the significance level set at $p < .05$. We computed partial eta squared (η_p^2) for effect size. According to Cohen (1988), partial eta squared of .01, .06 and .14 indicate small, medium and large effect sizes, respectively.

No part of the study analyses was pre-registered prior to the research being conducted.

Table 2 shows means and standard deviations on the four indices for our groups of participants.

Table 2. Mean z-scores on the four indices of specific functions (standard deviations shown in brackets)

	Schizophrenia patients			Healthy comparison participants		
	Young n=20	Middle n=17	Older n=25	Young n=20	Middle n=17	Older n=25
Shifting	-.011 (.641)	.052 (.565)	-.775 (.938)	.343 (.460)	.329 (.449)	.251 (.359)
Updating	.036 (.893)	-.337 (.673)	-.802 (.636)	.574 (.632)	.461 (.758)	.229 (.593)
Inhibition	.403 (.614)	.089 (.735)	-.528 (.931)	.382 (.432)	.136 (.606)	-.253 (.573)
Access	-.048 (.873)	-.460 (.807)	-.843 (.814)	.444 (.690)	.571 (.711)	.451 (.637)

3. Results

² For the inhibition score, we first computed a Z-score for HSCT which included time and errors before computing the inhibition score which included HSCT and SCWT, in order to give equal weight to both tests in the index. When necessary, Z-scores were recoded so that a high score reflected better performance.

Table 3 presents *F*-values, *p*-values and partial eta squared for the main analyses conducted in the study.

Table 3: *F*-values, *p*-values and partial eta squared for the main analyses conducted in the study.

	Main effect of Group			Main effect of Age			Group * Age Interaction		
	<i>F</i>	<i>p</i>	η_p^2	<i>F</i>	<i>p</i>	η_p^2	<i>F</i>	<i>p</i>	η_p^2
Shifting	24.51	<.001***	.172	7.67	<.001***	.115	5.00	.008**	.078
Access	46.46	<.001***	.282	3.13	.047*	.050	3.15	.046*	.051
Updating	38.71	<.001***	.247	8.20	<.001***	.122	1.39	.253	.023
Inhibition	.66	.417	.006	15.57	<.001***	.209	.59	.553	.010

Note. *** $p < .001$. ** $p < .01$. * $p < .05$. + $p < .10$

Figure 1 presents means and standard errors on the four indices for our groups of participants.

Figure 1: Z-scores for the four indices of executive functions (Panel A = Shifting, Panel B= Access, Panel C = Updating, Panel D = Inhibition) for schizophrenia patients and healthy comparison participants as a function of age group (error bars denote standard errors).

Shifting tasks:

The analysis conducted on the shifting index revealed significant effects of group [$F(1,118) = 24.51$; $p < .001$; $\eta_p^2 = .172$], age [$F(2,118) = 7.67$; $p < .001$; $\eta_p^2 = .115$] and age by group interaction [$F(2,118) = 5.00$; $p = .008$; $\eta_p^2 = .078$]. Performance was lower for patients and older participants, but the interaction revealed that the effect of age was only significant in patients [$F(2,59) = 8.16$; $p < .001$; $\eta_p^2 = .217$], not in comparison participants [$F(2,59) = .31$; $p = .73$]. Moreover, post-hoc tests indicated that the difference in patients with respect to the shifting index was significant only when comparing older patients to both younger ($p = .003$) and middle-aged patients ($p = .003$) but not when comparing younger and middle-aged patients ($p = .966$). Thus, these results argue strongly in favor of accelerated aging in schizophrenia patients, but only in older age.

Efficiency of access to memory:

The analysis performed on the access index revealed a significant effect of group [$F(1,118) = 46.46$; $p < .001$; $\eta_p^2 = .282$], age [$F(2,118) = 3.13$; $p = .047$; $\eta_p^2 = .050$] and the interaction between the two [$F(2,118) = 3.15$; $p = .046$; $\eta_p^2 = .051$]. Performance was lower for patients than comparison participants, and the interaction revealed that the effect of age was only significant in patients [$F(2,59) = 5.07$; $p = .009$; $\eta_p^2 = .147$], not in comparison participants [$F(2,59) = .21$; $p = .814$]. Moreover, post-hoc tests showed that the difference in patients with respect to the access index was only significant when comparing older patients to younger patients ($p = .006$), but not when comparing younger and middle-aged patients ($p = .298$), nor aged and middle-aged patients ($p = .316$). Even if the effect size is weak, these results therefore argue in favor of accelerated aging in schizophrenia patients as regards access to long-term memory.

322

323 *Updating tasks:*

324 The analysis performed on the updating index revealed a significant effect of group
325 [$F(1,118) = 38.71$; $p < .001$; $\eta_p^2 = .247$] and age [$F(2,118) = 8.20$; $p < .001$; $\eta_p^2 = .122$], but no
326 interaction between the two [$F(2,118) = 1.39$; $p = .253$]. Post-hoc tests in respect of the effect of age
327 yielded a significant difference between older and younger participants ($p < .001$) but only a
328 marginal difference between older and middle-aged participants ($p = .067$) and no difference
329 between younger and middle-aged participants ($p = .296$). In updating tasks, patients' performance
330 was impaired, and only older comparison participants had lower performance than younger
331 participants. However, the effect of age was no more deleterious in patients than in comparison
332 participants.

333

334 *Inhibition tasks:*

335 The analysis conducted on the inhibition index showed an effect of age [$F(2,118) = 15.57$; $p < .001$;
336 $\eta_p^2 = .209$], but no effect of group [$F(1,118) = .66$; $p = .417$], nor interaction [$F(2,118) = .59$;
337 $p = .553$]. Post-hoc tests showed that the effect of age was significant when comparing older patients
338 to both younger ($p < .001$) and middle-aged patients ($p = .003$) but not when comparing younger
339 and middle-aged patients ($p = .183$). Thus, inhibition abilities decrease in older participants, but in
340 the case of this measure schizophrenia patients were not impaired compared to healthy comparisons
341 participants.

342

343 **4. Discussion**

344 The aim of this study was to determine whether a particular specific executive function could be a
345 sensitive indicator of accelerated aging in schizophrenia. The main result is that accelerated aging
346 does not affect all of the four specific executive functions. According to the literature about normal

aging, shifting, updating and inhibition show age-related decline whereas access is preserved. In our sample, schizophrenia patients show the same cognitive deterioration as healthy comparison participants with regard to updating and inhibition. Thus, concerning these specific functions, schizophrenia patients appear normally affected by age. However, shifting and access were impaired in older schizophrenia patients, whereas in healthy comparison participants these functions were not affected by age, suggesting that age has a pathological effect on shifting and access in schizophrenia. The function most affected by age in schizophrenia is the shifting ability. Our results suggest that this function is not affected by age in middle-aged patients but is severely impaired in elderly patients. Access to long-term memory also showed accelerated aging. Even if the effect size is weaker than for shifting, suggesting this result needs replication, it seems important to note that the change with age is different. Contrary to shifting, which showed a decline only for older patients, the difference with respect to access was only significant between younger and older patients, suggesting an early accelerated age decline of access, and a late accelerated decline of shifting in patients. It should be noted that processing speed contributes to both shifting and access tasks (Fisk & Sharp, 2004; Neill & Rossell, 2013), and so it is possible processing speed may be the underlying factor explaining the accelerated aging in schizophrenia. Although processing speed is particularly involved in verbal fluency tests (Nuechterlein et al., 2008), the shift cost index used in the present study for shifting tasks should have reduce the influence of processing speed. Moreover, since processing speed is also involved in updating and inhibition, these functions should also show accelerated aging, which is not the case here. Thus, although processing speed contributes to executive performance, the present data lend greater weight to the idea that processing speed is not the main underlying factor explaining accelerated aging in schizophrenia. Further research is required to separate the contribution of processing speed more from executive performance in schizophrenia aging. Lastly, executive functions degradation in schizophrenia patients may accelerate before age of 65 against what was suggested for global cognition (J. I. Friedman et al.,

2001; Rajji & Mulsant, 2008). These results are of great interest for both research and clinical practice.

From a research perspective, the present results emphasize the need to consider the diversity of executive functions when studying cognition in schizophrenia, especially when looking for links between executive functions and other variables (such as medication or outcome). In fact, these relationships may be specifically linked to some functions but not to others and the use of general tests may lead to inaccurate conclusions. It seems that shifting and access abilities decline more rapidly in schizophrenia than in healthy comparison participants. This may explain, at least in part, the controversial results reported in the literature about schizophrenia aging in executive functions, insofar as with general executive tests it may be possible to observe impaired or preserved executive functioning in schizophrenia although some deficits may exist but are restricted to one or two domains. For instance, using only the Wisconsin Card Sorting Test, which is known to be strongly linked to shifting (Miyake et al., 2000), may produce a conclusion of accelerated aging in respect of executive functioning in schizophrenia (Fucetola et al., 2000), whereas it may hide some disparities among executive functions.

Moreover, the fact that, contrary to many studies (Laurenson et al., 2015; Westerhausen et al., 2011), we failed to observe an effect of the schizophrenia pathology on the inhibition index may reflect the considerable heterogeneity in schizophrenia patients. More specifically, previous studies using the HSCT also failed to report any difference between patients and healthy comparison participants (Chan et al., 2010; Laurenson et al., 2015), and data on the SCWT are controversial (Westerhausen et al., 2011). Another hypothesis to be taken into account is the interference index used in the SCWT (Perlstein, Carter, Barch, & Baird, 1998), given that an analysis conducted using the classical index indicated that schizophrenia patients showed less interference than comparison participants, whereas another interference index (more similar to the one we used) showed no group difference. As proposed by Li and Bosman (Li & Bosman, 1996), we therefore suggest that when assessing

SCWT in participants who may reflect cognitive slowing, such as older participants or psychiatric patients, it would be more thorough to use an index that takes account of these participants' higher baseline latency. A previous study (Donohoe et al., 2006) also indicated that inhibition is the only specific executive function that correlated with symptom severity, the suggestion being that inhibition in schizophrenia may be a very complex field showing high inter-individual heterogeneity. Thus, inhibition is probably not spared in schizophrenia but may be influenced by several possible confounders which can reduce statistical power.

According to previous researches showing that schizophrenia is a neurodevelopmental pathology (Meier et al., 2014; Sheffield et al., 2018), it is possible that white and grey matter deteriorations observed in schizophrenia patients (Orellana & Slachevsky, 2013; Zierhut et al., 2013) act as a vulnerability factor during late adulthood. The prefrontal cortex and its connections, which are already reduced in patients, would be even more affected by aging. More specifically, further researches may look at the effect of aging on the cingulate cortex and its connections with the prefrontal cortex in older schizophrenia patients. Indeed, abnormal connectivity has been observed between thalamus, anterior cingulate and dorsolateral prefrontal cortex in schizophrenia (Wagner et al., 2015), and the cingulate cortex is implicated in both shifting (Wilmsmeier et al., 2010) and access (Tyburski, Sokołowski, Cheć, Pełka-Wysiecka, & Samochowiec, 2015) tasks as well as in networks showing exaggerated vulnerability to aging in schizophrenia (Sheffield et al., 2016). Thus, evidence about accelerated aging in these regions would provide anatomic support about the accelerated aging in shifting and access tasks in schizophrenia.

As schizophrenia patients' longevity increases and because higher cognitive deficits increase the risk of dementia (Van Assche, Morrens, Luyten, Van de Ven, & Vandenbulcke, 2017), it is important to adapt remediation programs to the specificity of older patients. Improving cognition in these patients may have several benefits such as higher quality of life, autonomy and perhaps preventing from dementia. A program dedicated specifically to these patients should teach

compensatory strategies and develop exercises that deal with shifting, which are efficient in schizophrenia patients (Wykes et al., 2007), although some modifications are needed for it to be effective for older patients (Wykes et al., 2009). Concerning access, patients could be taught searching strategies (Martin, Wiggs, Lalonde, & Mack, 1994) and organizational strategies (Scheuringer, Wittig, & Pletzer, 2017) as a way of helping them to improve their memory. In this way, metacognitive approaches may be of interest, as monitoring skills training (Dunlosky, Kubat-Silman, & Hertzog, 2003) and memory strategies teaching (Troyer, 2001) has proved effective in healthy older participants. Moreover, a combination of these two components in a remediation program could yield unexpected results as shifting is closely associated with clustering in memory (Taconnat et al., 2009) and metamemory accuracy (Perrotin, Tournelle, & Isingrini, 2008).

Nevertheless, the inclusion of schizophrenia patients in remediation programs should account of our own results and those of previous studies (Rabanea-Souza et al., 2016; Raffard & Bayard, 2012; Wongupparaj et al., 2015) which argue for the assessment of specific executive functions as a complement to classical tests before a patient is admitted on a remediation program. Thus, given the considerable heterogeneity of patients' cognitive profiles (Raffard & Bayard, 2012), this would allow for better targeting of specific deficits as well as time-savings for patients who do not need to work on certain abilities.

This research has several strengths and limitations. First of all, to the best of our knowledge this is the first time the executive profile of older schizophrenia patients has been assessed with a validated model of executive functioning (Fisk & Sharp, 2004; Miyake et al., 2000). This method produces more accurate results concerning the cognitive deficit in schizophrenia and its course in later life. Moreover, only a few studies used strict pairing in respect of gender, age and education between patients and comparison participants despite the well-known effects of these variables on cognition and methodological recommendations (Fioravanti et al., 2012). Specifically, in the case of studies on aging, such demographic variables may interact as older participants often have fewer years of

education, there were more differences in women's education 60 years ago compared to now, and schizophrenia patients leave school earlier. Thus, thanks to the strict pairing in our study, effect sizes are often large even if our sample is relatively small. We were not able to control former patients' medication and to clarify the long-term effects of medication on cognitive functioning, which may be a recurrent problem in studies on schizophrenia aging (Suzuki, Gen, & Inoue, 2011). More precisely, second-generation antipsychotics have more beneficial effects on cognition than first-generation ones (Désaméricq et al., 2014; Guilera, Pino, Gómez-Benito, & Rojo, 2009; Keefe, Silva, Perkins, & Lieberman, 1999; Woodward, Purdon, Meltzer, & Zald, 2005), and older schizophrenia patients, unlike younger ones, may have been treated with first-generation antipsychotics for several years before the discovery of new treatments. Moreover, first-generation antipsychotics are often more prevalent in current treatment of older schizophrenia patients than in young patients. However, schizophrenia patients were treated in accordance with the guidelines for biological treatment of schizophrenia published by the World Federation of Societies of Biological Psychiatry (Hasan et al., 2012, 2013). They received stable doses for at least four weeks at inclusion and throughout the duration of the study, and most of the patients were administered only one antipsychotic which would presumably not result in excessive cognitive dysfunction. Schizophrenia patients also show a higher prevalence of tobacco smoking, and recent research shows that the long-term effects of tobacco smoking are deleterious on processing speed in patients (Vermeulen et al., 2018). Unfortunately, these results were not known by our team when the project started, and so these data were not taken into account. As processing speed influences other cognitive functions, especially the effect of aging on shifting abilities (Salthouse, Fristoe, McGuthry, & Hambrick, 1998), it is still possible that a long history of tobacco smoking in elderly patients partially influenced our results. The effect of past and current work status may also influence cognition (Ansiau, Marquié, Soubelet, & Ramos, 2005; Wilson et al., 2003), especially in a detrimental way for elderly participants who may have retired. However, taking this problem into account properly

(intellectual demands of the job, number of years worked, how long ago the participant stopped working, etc.) would be complex and should be investigated in future research. More specifically, such research should incorporate a measure including a large number of factors, such as the intellectual and physical demands of the job, modulated according to the number of years worked. Another potential criticism to this study is that comparison participants did not show age related effects on two specific executive functions. Although it seems normal for access which should not be affected by age (Fisk & Sharp, 2004), it is more uncommon for shifting. Even if some studies didn't find age effect on plus-minus task (Etienne, Marin-Lamellet, & Laurent, 2008) or number-letter task (Delaloye et al., 2009), we acknowledge that our participants were not as old as typically found in normal aging studies. This may explain the failure to show age-related effects on shifting in comparison participants despite a decrease in healthy older participants' performance. However, schizophrenia patients have higher mortality rates than general population (Lee et al., 2018) so that recruiting patients older than 70 would be very difficult and not representative of this population. We therefore chose age groups according to the literature on schizophrenia (Fucetola et al., 2000) and to keep strict pairing for comparison participants. The term "accelerated aging" may therefore appear inappropriate as healthy participants did not show age effects on these functions. However age-related effects on shifting are well documented (Clarys et al., 2009; Fisk & Sharp, 2004; Schnitzspahn et al., 2013) which is not the case for access (Fisk & Sharp, 2004). Thus, the term "pathologic aging" might be more appropriate for age-related effects on access in schizophrenia. Finally, as Anxiety and Depressions scores did not correlate with all of the specific executive functions, we decided not to include these scores in the analyses to make them easier to understand. However, we conducted the same analyses with entering Anxiety and Depression as covariates to find out whether these variables may alter the results. This was the case only for the interaction between Schizophrenia and Age on Access index which turned marginal (from $p = .046$ to $p = .051$) when the depression score was entered as a covariate. While we acknowledge that depression scores

may contribute to the interaction between Schizophrenia and Age on Access, the difference between the two p-values is relatively small. Moreover, since higher depression scores are common in schizophrenia patients, controlling for these symptoms may hide part of the pathology.

5. Conclusions

This study emphasizes the importance of considering the diversity of executive functions in schizophrenia. In this way, our results indicate that shifting shows early accelerated aging and access to long-term memory shows late pathologic decline, whereas updating and inhibition did not show accelerated aging. Thus, specific executive functions should be evaluated before admitting patients on remediation programs, which ought to be adapted to older patients.

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