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## **Executive functions in schizophrenia aging: Differential effects of age within specific executive functions**

Flavien Thuaire, Fabien Rondepierre, Elisabeth Bacon, Guillaume T. Vallet,  
Isabelle Jalenques, Marie Izaute

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

3  
4 **Authors and affiliations.**  
5 Flavien Thuaire<sup>a</sup>, Fabien Rondepierre<sup>b</sup>, Elisabeth Bacon<sup>c</sup>, Guillaume T. Vallet<sup>a</sup>, Isabelle Jalenques<sup>d</sup>,  
6 Marie Izaute<sup>a1</sup>

7  
8 <sup>a</sup> Université Clermont Auvergne, CNRS, LAPSCO, F-63037 Clermont-Ferrand, France.  
9 <sup>b</sup> Service de Psychiatrie de l'Adulte A et Psychologie Médicale, Centre Mémoire de Ressources et  
10 de Recherche, CHU Clermont-Ferrand, Clermont-Ferrand, France.  
11 <sup>c</sup> INSERM U-1114, Fédération de Médecine Translationnelle de Strasbourg (FMTS), CHU de  
12 Strasbourg, Université de Strasbourg, France.  
13 <sup>d</sup> Service de Psychiatrie de l'Adulte A et Psychologie Médicale, Centre Mémoire de Ressources et  
14 de Recherche, CHU Clermont-Ferrand, Institut de Psychiatrie-GDR 3557, Université Clermont  
15 Auvergne, Clermont-Ferrand, France.

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<sup>1</sup> **Corresponding author:** Marie Izaute LAPSCO, UMR CNRS 6024, 34 avenue Carnot, 63037 Clermont-Ferrand, France  
Telephone: + 33 4 73 40 62 55 – Fax: + 33 4 73 40 64 82  
E-mail: [marie.izaute@uca.fr](mailto:marie.izaute@uca.fr)

29

30 **Abstract**

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

38 20 younger (age 18-34), 17 middle-aged (age 35-49) and 25 older (age 59-76) schizophrenia patients  
39 and 62 healthy comparison participants matched for gender, age and education performed a  
40 neurocognitive battery evaluating the four specific executive functions.

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

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

50

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

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## 55 **1. Introduction:**

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

68 Moreover, recent findings suggest that schizophrenia is a neurodevelopmental disorder with  
69 cognitive impairments exhibited prior to the onset of the pathology (Meier et al., 2014; Sheffield,  
70 Karcher, & Barch, 2018). Cortical dysfunctions are observed during executive tasks including  
71 reduced activations in the prefrontal cortex, anterior cingulate cortex and thalamus (Minzenberg,  
72 Laird, Thelen, Carter, & Glahn, 2009). Recent studies also observed structural deterioration of white  
73 matter in networks involving the prefrontal cortex (Orellana & Slachevsky, 2013; Wagner et al.,  
74 2015). Thus, despite the heterogeneity of the findings concerning cortical dysfunctions in  
75 schizophrenia, impairment in prefrontal functioning, which is historically linked to executive  
76 functioning (Luria, 1966; Shallice, 1982), is consistently observed.

77 Executive functions are composed of multiple sub-functions which may be grouped together in three  
78 specific functions that are independent of each other but also correlated to the general concept of  
79 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

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

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

130 is therefore possible that aging has more deleterious effects in schizophrenia patients than in healthy  
131 people. Thus, it is of special interest to ascertain whether cognitive deficits in schizophrenia patients  
132 increase more with aging than is the case with healthy participants. This knowledge is necessary to  
133 adapt treatments and cognitive remediation programs for older patients. Schizophrenia patients  
134 show accelerated physical aging (Jeste, Wolkowitz, & Palmer, 2011), including for their brain  
135 (Schnack et al., 2016; Sheffield et al., 2016) compared to healthy controls of the same age. Studies  
136 are less consistent, however, concerning neurocognition which is linked to adaptive functioning  
137 (Green, 2016; Harvey et al., 1999), quality of life (Mohamed et al., 2008), and social and everyday  
138 living skills (Evans et al., 2003; Kalache et al., 2015; McClure et al., 2007). Some authors observed  
139 accelerated aging only with executive functions (Fucetola et al., 2000; Herold et al., 2017), whereas  
140 others indicated that it did not affect executive functions at all, but processing speed and verbal  
141 learning (Loewenstein, Czaja, Bowie, & Harvey, 2012), or visuo-spatial functions (Stirling et al.,  
142 2003) instead. The results of a meta-analysis failed to report accelerated aging (Irani, Kalkstein,  
143 Moberg, & Moberg, 2011) on several functions, including executive functions, and the authors of  
144 another study even observed a normalization of cognition with aging in schizophrenia patients (Irani  
145 et al., 2012). Several factors may account for these controversial results, including the kind of tasks  
146 used to measure cognition, whether or not patients are institutionalized (Bowie, Reichenberg,  
147 McClure, Leung, & Harvey, 2008), task difficulty (Knapp, Viechtbauer, Leonhart, Nitschke, &  
148 Kaller, 2017) and, more critically, the age of the older patients included in the study (J. I. Friedman  
149 et al., 2001; Rajji & Mulsant, 2008).

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

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

161

## 162 **2. Methods and material**

### 163 *2.1. Participants*

164 We report how we determined our sample size, all data exclusions (if any), all data  
165 inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data  
166 analysis, all manipulations, and all measures in the study. This study was conducted in accordance  
167 with ethical standards and had the approval of the local ethics committees (EudraCT 2010-A00857-  
168 32 and PRI 2000, HUS N°2326). Before the investigation started, all the participants provided  
169 written informed consent after receiving a full explanation about the study. The participants were  
170 62 clinically-stable outpatients with schizophrenia recruited from the Psychiatric Department of the  
171 University Hospital. The following inclusion/exclusion criteria were established prior to data  
172 analysis, and all manipulations and measurements performed in the study. According to the  
173 consensus opinion of their current psychiatrist and a senior psychiatrist on the research team, all of  
174 the patients met the criteria for schizophrenia as set out in the Diagnostic and Statistical Manual of  
175 Mental Disorders -IV-TR. Patients with any current co-morbid neurologic or psychiatric disorder,  
176 including alcohol or substance abuse or dependence, were not included. Their psychiatric symptoms  
177 were assessed according to the Positive And Negative Symptoms Scale (PANSS) (Kay, Fiszbein,  
178 & Opler, 1987). Anxiety and depression were screened using the Hospital Anxiety and Depression  
179 Scale (HADS) (Zigmond & Snaith, 1983). Verbal intelligence quotient (IQ) was evaluated using



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

195

196 Table 1. Demographic characteristics of patients with schizophrenia and comparison participants by  
 197 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) <sup>b</sup>	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 <sup>a, b</sup>	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 <sup>a, b</sup>	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 <sup>a, b</sup>	83.2 (18.5)	85.9 (16.3)	89.8 (12.1)	90.7 (14.8)	94.8 (11.9)	108.9 (12.9)

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

199 <sup>a</sup> significant group difference between patients and comparison participants

200 <sup>b</sup> significant age difference

201

## 202 **2.2. Material**

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

209

210 The scores used in the analyses consisted of:

### 211 *2.2.1 Shifting tasks:*

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

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

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

226

#### 227 *2.2.2. Access tasks:*

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

230

#### 231 *2.2.3. Updating tasks:*

232 *N-back task* (Clarys, Bugajska, Tapia, & Baudouin, 2009; Perrotin, Belleville, & Isingrini, 2007):

233 A list of 30 letters was read out to the participants, who were instructed to say aloud (yes/no) whether  
234 the current letter was the same as one of the three previous letters. To simplify the instructions for  
235 the older patients, participants were asked to compare the current letter not with one letter occurring  
236 earlier in the sequence but with the 3 previous letters. The next letter was read after the participant’s  
237 response. The score was the number of correct answers (hits and correct rejections). As there was  
238 no 0-back control condition, working memory performance cannot be separated from lower order  
239 functions.

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

244

#### 245 *2.2.4. Inhibition tasks:*

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

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

257

### 258 **2.3. Data analyses**

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

260 Not all participants completed all the tests: 5 (4%) didn't complete the plus minus test (3 young  
261 patients, 1 middle-aged patient and 1 older patient), 1 (0.8%) the n-back test (1 older patient) and  
262 10 (8%) the HSCT (1 young patient, 1 middle-aged patient, 6 older patients and 2 older comparison  
263 subjects). The missing data were replaced using Multiple Imputation by Chained Equations  
264 (MICE)<sup>1</sup>.

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

---

<sup>1</sup> 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.

267 computed Z-scores for each task and then calculated the means between the two tests within each  
 268 of the four executive domains (shifting, updating, inhibition and access) to create a composite index  
 269 for these cognitive abilities<sup>2</sup>. We then ran separate Analyses Of Variance (ANOVAs) on each index  
 270 with Group and Age as independent variable. Tukey’s test was used as a post-hoc test when age  
 271 effects were observed.

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

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

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

277

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

279

280 Table 2. Mean z-scores on the four indices of specific functions (standard deviations shown in  
 281 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)

282

283

284

### 285 3. Results

<sup>2</sup> 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.

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

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

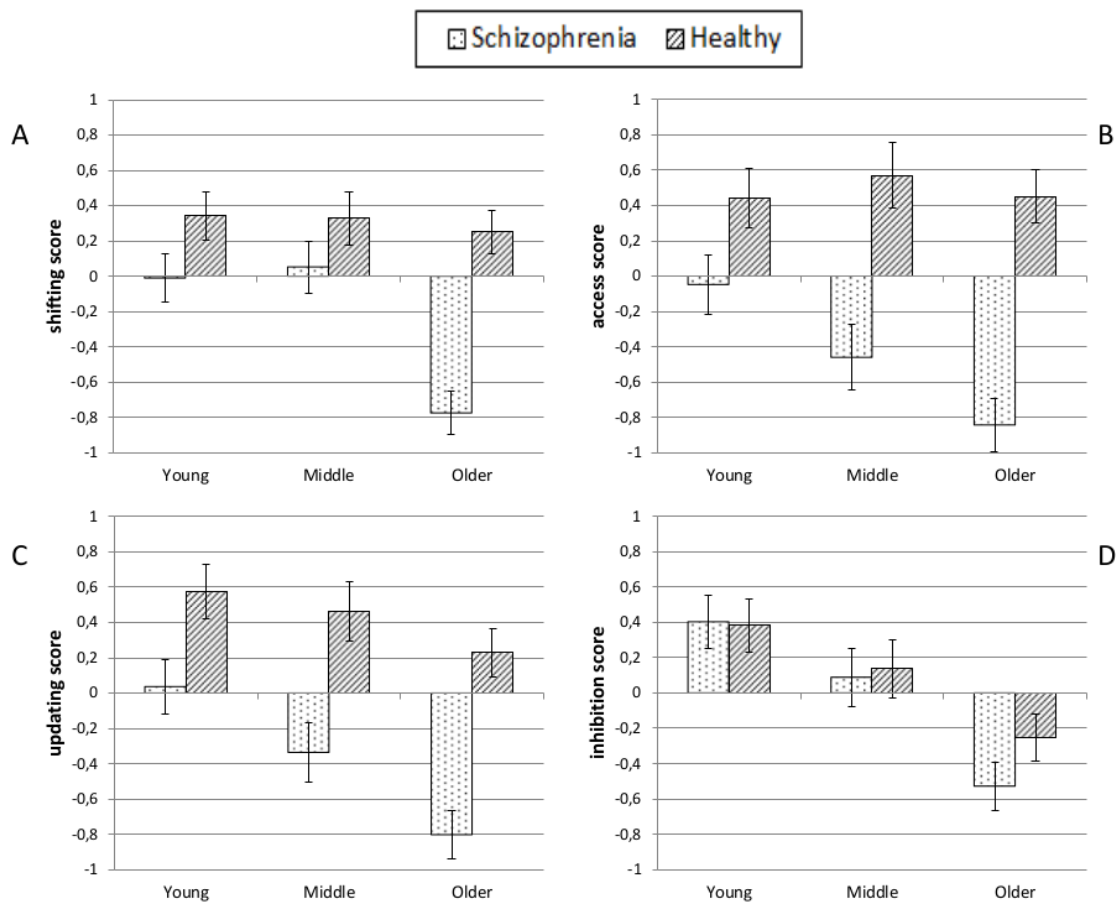
	Main effect of Group			Main effect of Age			Group * Age Interaction		
	<i>F</i>	<i>p</i>	$\eta_p^2$	<i>F</i>	<i>p</i>	$\eta_p^2$	<i>F</i>	<i>p</i>	$\eta_p^2$
Shifting	24.51	<.001***	.172	7.67	<.001***	.115	5.00	.008**	.078
Access	46.46	<.001***	.282	3.13	.047*	.050	3.15	.046*	.051
Updating	38.71	<.001***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

289 Note. \*\*\* *p* < .001. \*\* *p* < .01. \* *p* < .05. + *p* < .10  
 290

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

292

293



294

295 Figure 1: Z-scores for the four indices of executive functions (Panel A = Shifting, Panel B= Access,  
296 Panel C = Updating, Panel D = Inhibition) for schizophrenia patients and healthy comparison  
297 participants as a function of age group (error bars denote standard errors).  
298

299

300 *Shifting tasks:*

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

310

311 *Efficiency of access to memory:*

312 The analysis performed on the access index revealed a significant effect of group [ $F(1,118) = 46.46$ ;  
313  $p < .001$ ;  $\eta_p^2 = .282$ ], age [ $F(2,118) = 3.13$ ;  $p = .047$ ;  $\eta_p^2 = .050$ ] and the interaction between the two  
314 [ $F(2,118) = 3.15$ ;  $p = .046$ ;  $\eta_p^2 = .051$ ]. Performance was lower for patients than comparison  
315 participants, and the interaction revealed that the effect of age was only significant in patients  
316 [ $F(2,59) = 5.07$ ;  $p = .009$ ;  $\eta_p^2 = .147$ ], not in comparison participants [ $F(2,59) = .21$ ;  $p = .814$ ].  
317 Moreover, post-hoc tests showed that the difference in patients with respect to the access index was  
318 only significant when comparing older patients to younger patients ( $p = .006$ ), but not when  
319 comparing younger and middle-aged patients ( $p = .298$ ), nor aged and middle-aged patients  
320 ( $p = .316$ ). Even if the effect size is weak, these results therefore argue in favor of accelerated aging  
321 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



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

372 2001; Rajji & Mulsant, 2008). These results are of great interest for both research and clinical  
373 practice.

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

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

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

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

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

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

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

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

447 education, there were more differences in women's education 60 years ago compared to now, and  
448 schizophrenia patients leave school earlier. Thus, thanks to the strict pairing in our study, effect  
449 sizes are often large even if our sample is relatively small. We were not able to control former  
450 patients' medication and to clarify the long-term effects of medication on cognitive functioning,  
451 which may be a recurrent problem in studies on schizophrenia aging (Suzuki, Gen, & Inoue, 2011).  
452 More precisely, second-generation antipsychotics have more beneficial effects on cognition than  
453 first-generation ones (Désaméricq et al., 2014; Guilera, Pino, Gómez-Benito, & Rojo, 2009; Keefe,  
454 Silva, Perkins, & Lieberman, 1999; Woodward, Purdon, Meltzer, & Zald, 2005), and older  
455 schizophrenia patients, unlike younger ones, may have been treated with first-generation  
456 antipsychotics for several years before the discovery of new treatments. Moreover, first-generation  
457 antipsychotics are often more prevalent in current treatment of older schizophrenia patients than in  
458 young patients. However, schizophrenia patients were treated in accordance with the guidelines for  
459 biological treatment of schizophrenia published by the World Federation of Societies of Biological  
460 Psychiatry (Hasan et al., 2012, 2013). They received stable doses for at least four weeks at inclusion  
461 and throughout the duration of the study, and most of the patients were administered only one  
462 antipsychotic which would presumably not result in excessive cognitive dysfunction. Schizophrenia  
463 patients also show a higher prevalence of tobacco smoking, and recent research shows that the long-  
464 term effects of tobacco smoking are deleterious on processing speed in patients (Vermeulen et al.,  
465 2018). Unfortunately, these results were not known by our team when the project started, and so  
466 these data were not taken into account. As processing speed influences other cognitive functions,  
467 especially the effect of aging on shifting abilities (Salthouse, Fristoe, McGuthry, & Hambrick,  
468 1998), it is still possible that a long history of tobacco smoking in elderly patients partially  
469 influenced our results. The effect of past and current work status may also influence cognition  
470 (Ansiu, Marquié, Soubelet, & Ramos, 2005; Wilson et al., 2003), especially in a detrimental way  
471 for elderly participants who may have retired. However, taking this problem into account properly

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

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

500

## 501 **5. Conclusions**

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

507

508

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510

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512 Investigation, Methodology, Writing – original draft, Writing – review & editing. **Fabien**  
513 **Rondepierre:** Data curation, Resources, Visualization, Writing – review & editing. **Elisabeth**  
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