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## **Executive deficits in schizophrenia: mediation by processing speed and its relationships with aging**

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1 Executive deficits in schizophrenia: Mediation by processing speed and its relationships with  
2 aging

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16 **Abstract**

17 **Background:** Executive deficits are a core characteristic of schizophrenia. Yet, the origin of  
18 these impairments remains unclear as they may be caused by processing slowing. This issue is  
19 of particular interest for aging insofar as cognitive aging is also associated with decline in  
20 executive functioning and a slowing of processing speed. As schizophrenia patients' life  
21 expectancy increases, a better understanding of the origin of older patients' cognitive deficits  
22 becomes essential so that healthcare can be adapted to suit them. This study aims to determine  
23 whether processing speed mediates how schizophrenia affects executive functions, and whether  
24 these relationships are moderated by age.

25 **Methods:** Sixty-two schizophrenia patients (27 women) and 62 healthy comparison subjects  
26 matched for age (range: 18 to 76 years), gender and education performed neurocognitive tests  
27 to evaluate their executive functions (shifting, updating, inhibition and access) and processing  
28 speed.

29 **Results:** Processing speed mediated the effect of schizophrenia on the four specific executive  
30 functions, and age moderated this mediation for shifting, updating and access, but in different  
31 ways. Age moderated the effect of processing speed on shifting, the direct effect of  
32 schizophrenia on access, and both the effect of processing speed and direct effect of  
33 schizophrenia on updating.

34 **Conclusions:** This research highlights the need to evaluate processing speed routinely during  
35 therapeutic follow-up, as it is easy and simple to assess and appears to be at the heart of the  
36 cognitive deficits in schizophrenia. Finally, processing speed abilities yield information about  
37 the evolution of cognition with aging in schizophrenia.

38

39 **Key Words:** Schizophrenia; Adulthood; Aging; Processing speed; Executive functions;  
40 Miyake's model.

## 41 **Introduction**

42 Cognitive impairment is a core feature of schizophrenia and affects most cognitive domains  
43 (Heinrichs & Zakzanis, 1998; Mesholam-Gately et al., 2009). Deficits appeared even before the  
44 onset of schizophrenia (Meier et al., 2014) and patients' decline in later life is strongly related  
45 to their functional competences (Harvey et al., 1999; Kalache et al., 2015). An important issue  
46 in the study of schizophrenia is that both executive functions (EFs) (Reichenberg & Harvey,  
47 2007) and processing speed (PS) (Dickinson et al., 2007) are impaired, and that these deficits  
48 may affect other cognitive abilities. However, despite the increase in schizophrenia patients'  
49 life expectancy (Cohen et al., 2008; E. E. Lee et al., 2018), the course of cognitive impairment  
50 in late adulthood remains unclear owing to the lack of studies that investigate this particular  
51 issue (Herold et al., 2017; Rajji & Mulsant, 2008), and because normal aging is also associated  
52 with cognitive decline (Cona et al., 2013; Verhaeghen & Cerella, 2002). However, knowledge  
53 is crucial for adapting treatments and cognitive remediation to older schizophrenia patients.  
54 Given that remediation programs are currently better suited to younger patients, they need to  
55 be adapted to the specificity of older patients (Wykes et al., 2009).

56 EFs allow adapting behavior to diverse situations (e.g. creating a plan, initiating its execution,  
57 persevering until completion). They also mediate our ability to organize our thoughts in a  
58 targeted manner (Jurado & Rosselli, 2007). In other words, they are regarded as higher order  
59 cognitive processes supporting other areas of cognition and thus are widely used in everyday  
60 life. Although executive functioning covers broad concepts, the importance of considering  
61 some specific EFs is now well established. The common distinction proposed identifies three  
62 specific EFs, namely shifting, updating and inhibition (Miyake et al., 2000). Subsequently, Fisk  
63 & Sharp (2004) identified a fourth function, referred to as "access", which reflects the efficiency  
64 of access to long-term memory and may be assessed with word fluency tests.

65 Executive deficits in schizophrenia are well established (Fioravanti et al., 2012). A more fine-  
66 grained analysis of these deficits revealed impairments in shifting, updating and inhibition  
67 (Chan et al., 2006; Donohoe et al., 2006; Rabanea-Souza et al., 2016; Raffard & Bayard, 2012;  
68 Wongupparaj et al., 2015) as well as access (Rossell, 2006), even though there were some  
69 discrepancies concerning inhibition (Chan et al., 2010; Laurenson et al., 2015; Thuaire et al.,  
70 2020; Westerhausen et al., 2011). Importantly, insofar as EFs are strongly linked to everyday  
71 life skills (McClure et al., 2007) and quality of life (Tolman & Kurtz, 2012) in schizophrenia,  
72 they are an important target area for cognitive remediation (Penadés et al., 2010).

73 Nevertheless, it remains unclear whether executive impairment in schizophrenia comes from  
74 an executive impairment *per se* or from low-order processes instead. Contrary to executive  
75 functioning, which is thought to be uniquely human (Luria, 1966) or at least specific to the most  
76 intelligent species, lower-order processes are less evolved as cognitive functions. Those such  
77 as PS are implicated in almost every cognitive process. Thus, complex operations need to  
78 process simple operations quickly in order to keep their product available (Salthouse, 1996).

79 Consequently, PS and EFs share some mutual variance (Albinet et al., 2012) but tap into  
80 different processes. Indeed, some authors suggested that PS is be the most important deficit in  
81 patients (Dickinson et al., 2007) and may mediate EFs impairments (Rodríguez-sánchez et al.,  
82 2007). Accordingly, it was shown in schizophrenia that PS contributed significantly to  
83 executive functioning (Raffard & Bayard, 2012), even when the executive tests used were not  
84 time-constrained (Ojeda et al., 2012). Yet, it is worth mentioning that PS does not account for  
85 all the deficits in EFs (Neill & Rossell, 2013), and its statistical control does not cancel out the  
86 deficits in all measures of EFs (Savla et al., 2011). Thus, the relationships between PS and EFs  
87 may be very complex, as PS seems to mediate some executive deficits, although the analyses  
88 conducted in previous studies were not designed as accurate tests for mediation. Moreover, as  
89 both EFs and PS declined severely in healthy aging and appear to play a distinctive role in

90 explaining age-related deficits (Albinet et al., 2012; T. Lee et al., 2012), we surmised that  
91 participants' age would be a good criterion for supplementing our knowledge about this  
92 mediation.

93 Indeed, as EFs and PS are both impaired in healthy aging and in schizophrenia, some studies  
94 looked at whether these processes would show accelerated aging. Accelerated aging means that  
95 age effects would be greater in patients than in healthy participants. Some of the studies which  
96 examined this question in terms of executive functioning concluded in favor of the existence of  
97 accelerated aging (Fucetola et al., 2000; Herold et al., 2017), while others did not (Irani et al.,  
98 2011; Loewenstein et al., 2012; Stirling et al., 2003). To shed some light on these controversial  
99 results, in a previous article our team analyzed the performances of young, middle-aged and  
100 older schizophrenia patients and healthy comparison participants in neuropsychological tests  
101 assessing the four specific EFs (Thuairé et al., 2020). The results showed that accelerated aging  
102 was observed for shifting, and that access was impaired in older schizophrenia patients.  
103 However, updating and inhibition were not more affected by the pathology with aging.  
104 Similarly, studies about the effects of accelerated aging on PS in schizophrenia are conflicting.  
105 One study found accelerated aging in Trail-Making-Test Part A (TMT-A) and digit symbol  
106 (Loewenstein et al., 2012), whereas another found it in TMT-A but not digit symbol (Bowie et  
107 al., 2008), and a third study showed no accelerated aging in TMT-A (Herold et al., 2017). It is  
108 therefore not clear from the literature whether aging increases executive deficits and/or the  
109 cognitive slowing of schizophrenia patients in comparison to healthy participants. In light of  
110 the results of our previous work (Thuairé et al., 2020) and studies showing a link between PS  
111 and EFs performance (Neill & Rossell, 2013; Raffard & Bayard, 2012; Savla et al., 2011), one  
112 possibility might be that PS mediates some EFs and that such mediation may have different  
113 strengths according to specific EFs. Moreover, aging may have different effects on this  
114 mediation as a function of specific EFs.

115 Thus, we set out to analyze our previous study further to determine which specific EFs are  
116 strongly mediated by PS because such knowledge will help remediation programs target the  
117 root causes of the executive deficits. We hypothesized that PS would mediate the four specific  
118 EFs but with different strengths. Moreover, we wanted to ascertain whether age could be a  
119 moderator of these mediation effects in order to help adapt remediation programs to strengths  
120 and weaknesses specific to older patients. According to our previous study showing increased  
121 deficits in older patients for shifting and access (Thuairé et al., 2020), we surmised that age  
122 would moderate this mediation only for these functions. This result lends further weight to the  
123 arguments in support of the specificity of schizophrenia aging and the need to adapt remediation  
124 programs to older patients (Wykes et al., 2009).

125

## 126 **Methods and material**

### 127 *Participants*

128 The present study involves the same participants as those recruited and described in our  
129 previous study (Thuairé et al., 2020).

130 This study was conducted in accordance with ethical standards and with the approval of the  
131 local ethics committees (EudraCT 2010-A00857-32 and PRI 2000, HUS N°2326). Before the  
132 investigation started, and after receiving a full explanation about the study, all the participants  
133 gave their informed consent in writing. They were 62 clinically-stable outpatients with  
134 schizophrenia recruited from the Psychiatric Departments of the University Hospitals. Patients  
135 with any current co-morbid neurologic or psychiatric disorder, including alcohol or substance  
136 abuse or dependence, were not included. Their psychiatric symptoms were assessed according  
137 to the Positive And Negative Symptoms Scale (PANSS, Kay *et al.* 1987). They were screened  
138 for anxiety and depression using the Hospital Anxiety and Depression Scale (HADS, Zigmond  
139 & Snaith 1983). Verbal intelligence quotient (IQ) was evaluated using vocabulary and

140 arithmetic tests taken from the Wechsler Adult Intelligence Scale, revised (WAIS-R, Silverstein  
141 1982). Patients received stable doses of psychotropic medication for at least 4 weeks. In  
142 addition, 62 healthy comparison participants matching the patients in terms of age, gender and  
143 education were recruited from the community. None of these participants had a known  
144 neurological or psychiatric affliction or was currently suffering or had suffered in the past from  
145 alcohol or substance abuse or dependence. The age of the participants ranged from 18 to 76  
146 years.

147 Table 1 presents the demographical, clinical and descriptive statistics of the group comparison  
148 data.

149

150

### 151 ***Material***

152 EFs were assessed according to the framework proposed by Miyake *et al.* (2000), which  
153 distinguishes three specific EFs (shifting, updating and inhibition), with the addition of Fisk  
154 and Sharp (2004) for efficiency of access to long-term memory. Two tests were used for each  
155 specific function, and a further two tests were also used to assess PS. See the supplement for a  
156 more detailed description of the tests.

157 The scores used in the analyses consisted of:

#### 158 *Shifting tasks:*

159 *Plus-minus task* (Jersild, 1927; Spector & Biederman, 1976): Participants had to switch between  
160 adding and subtracting 3 in respect of different numbers. The shift cost was calculated as the  
161 difference between the time taken to complete the third list and the average for the first and  
162 second lists:  $T3 - [(T2 + T1) / 2]$ .



163 *Number-letter task* (Rogers & Monsell, 1995): Participants had to switch between processing  
164 consonants and vowels. The shift cost was calculated in the same way as in the plus-minus test:  
165  $T3 - [(T2 + T1) / 2]$ .

166

167 *Updating tasks:*

168 *N-back task*: Participants had to remember and update in memory only the last three letters said  
169 by the experimenter to decide whether each new one was the same as one of the three previous  
170 letters. The score was the number of correct answers (hits and correct rejections).

171 *Self-Ordered Pointing Task* (Petrides & Milner, 1982): Participants had to update in memory  
172 the drawings they chose, in order not to choose them anymore. The score was the number of  
173 different drawings selected.

174

175 *Inhibition tasks:*

176 *Stroop color word task* (SCWT, Stroop 1935), card version: Participants had to inhibit word  
177 reading in order to name the color of the ink used for words depicting colors. To reduce the  
178 potential bias of patients' cognitive slowing, we used the interference score proposed by (Li &  
179 Bosman, 1996):  $(\text{Baseline} - \text{color word}) / \text{Baseline}$ .

180 *Hayling sentence Completion Test* (HSCT, Burgess & Shallice 1996): Participants had to inhibit  
181 the final word of sentences and say aloud a word that was not linked in any way with either the  
182 sentence or final word. The scores were the time taken to complete Part B and the number of  
183 errors in Part B.

184

185 *Access tasks:*

186 *Verbal fluency*: Participants had to say aloud as many words as they could according to a  
187 phonemic or semantic rule. Two verbal fluency tasks were assessed, namely phonemic fluency

188 (Letter P) and semantic fluency (category “animals”). The score was the number of correct  
189 words in 60 seconds.

190

191 *Processing speed tasks:*

192 *Digit copying test* (Weschler, 1989): Participants had to write down the digit matching a  
193 number according to a key. The score was the number of items correctly reported in 30 seconds.

194 This time limit was chosen to reduce the impact of executive abilities and memory on  
195 performance (Knowles et al., 2015).

196 *Letter comparison test:* On a sheet of paper displaying pairs of X and O, participants had to  
197 decide whether each pair was identical or different and to tick the corresponding box. The score  
198 was the number of correct items in 30 seconds.

199

## 200 **Data analyses**

201 Data used in this article are available at: <https://osf.io/ebn5a/>

202 Not all of the participants completed all the tests: 5 failed to complete the plus minus test (4%),  
203 1 the n-back test (0.8%), and 10 the HSCT (8%). The missing data were replaced using Multiple  
204 Imputation by Chained Equations (Azur et al., 2011). See Thuaire et al., (2020) for more details.  
205 Z-scores were computed for each task, based on mean and standard deviation of all participants,  
206 after which the means were calculated between the two tests in each of the four executive  
207 domains (shifting, updating, inhibition and access) and PS, to create a composite index for these  
208 cognitive abilities<sup>1</sup>.

209 All analyses were run on SPSS Statistics 25 (IBM Corp, 2017), running the PROCESS script  
210 to test the mediation (Hayes, 2018). Mediation signifies that the effect of an independent

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<sup>1</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. Where necessary, Z-scores were re-coded, so that a high score reflected better performance.

211 variable (IV) on a dependent variable (DV) is at least partly driven by a mediator (M). Several  
212 effects are calculated by means of regression analyses: (*a*) is the effect of the IV on M; (*b*) is  
213 the effect of M on the DV when controlling for the effect of the IV; (*c*) is the **total effect** of the  
214 IV on the DV and is the sum of a **direct effect** (*c'*) of the IV on the DV and an **indirect effect**  
215 (*a x b*) which is the effect of the IV on the DV through M. As regression analyses cannot test  
216 the significance of the indirect effect (*a x b*), the latter is tested using a bias-corrected  
217 bootstrapping approach (n = 5,000 bootstrap samples (Preacher & Hayes, 2008)). Thus, if zero  
218 is not in the 95% confidence interval, we can conclude that the indirect effect is significantly  
219 different from zero. Moderated mediation means that a moderator (W) affects at least one path  
220 of the mediation relation. The effect of one variable on another may therefore be different  
221 according to the value of the moderator. Group (0= Comparison participants, 1= Schizophrenia  
222 patients) was the IV, PS was the mediator, age was the moderator, and the four specific EFs  
223 were entered as DVs in separate analyses. Thus, the total effect is the effect of schizophrenia  
224 on a specific EF without taking into account a possible effect of PS. The direct effect is the  
225 effect of schizophrenia on a specific EF after controlling for the effect of PS, and the indirect  
226 effect is the effect of PS on a specific EF after controlling for the effect of schizophrenia.  
227 Unstandardized coefficients (B) are reported in the analyses.

228

## 229 **Results:**

230 Table 2 presents means and standard deviations on the five indices for schizophrenia patients  
231 and healthy comparisons participants.

232 Table S1 presents intercorrelations among all study variables. All variables were significantly  
233 correlated with each other, except Group with Age, Group with Inhibition and Age with Access.

234

235 Mediation analyses

236 Figure 1 shows the results of the mediation analyses about the effect of schizophrenia on the  
237 four specific EFs through PS. Path (*a*) indicates that schizophrenia had a strong negative effect  
238 on PS. Path (*b*) shows that higher PS increases performance in the four EFs. Mediation (*a x b*)  
239 was significant for the four EFs, indicating that PS mediated the four EFs. Total effects of  
240 schizophrenia on EFs (*c*) were significant for shifting, updating and access, whereas direct  
241 effects of schizophrenia controlling for PS (*c'*) only remained significant for updating and  
242 access.

243

244 Moderated mediation analyses

245 Moderation on a mediation model may be present in 3 paths: on the effect of the IV on M (path  
246 *a*), on the effect of M on the DV when controlling for the effect of the IV (path *b*), and the direct  
247 effect of the IV on the DV (path *c'*). However, as, despite a significant deleterious effect of age  
248 on PS ( $B = -.029, p < .001$ ), there was no moderation effect of age on path *a* ( $B = -.010,$   
249  $p = .197$ ), further analyses focus only on paths *b* and *c'*. Figure 2 shows the significant  
250 moderation effects of age on the mediation of the effect of schizophrenia on shifting (Panel A),  
251 updating (Panel B) and Access (Panel C) through PS. As may be seen in Figure 2, age  
252 moderated the mediation of schizophrenia on three out of the four EFs, but in different ways.

253

254 *Moderation by age of the mediation by speed of the group effect on shifting:*

255 Conditional process analyses using PROCESS macro revealed that only path *b* was significantly  
256 moderated by age ( $B = .011, p = .002$ ). Thus, the effect of PS on shifting abilities is moderated  
257 by age in such a way that the effect of speed on shifting is greater in older participants.  
258 Therefore, schizophrenia patients, whose PS is slower, are more affected by age when it comes

259 to shifting abilities. Figure S1 shows the effects of age on shifting as a function of participants'  
260 PS.

261

262 *Moderation by age of the mediation by speed of the group effect on updating:*

263 PROCESS showed that both paths  $b$  ( $B = -.011, p = .045$ ) and  $c'$  ( $B = -.022, p = .030$ ) were  
264 significantly moderated by age. Thus, concerning path  $b$ , the effect of PS on shifting abilities is  
265 less in older participants and, consequently, for schizophrenia patients, whose processing  
266 performance is lower, older patients' updating performance would be less affected than that of  
267 younger patients. However, a counterbalancing effect is observed on path  $c'$  as age increases  
268 the effect of schizophrenia on updating, leading older schizophrenia patients to record a lower  
269 updating performance. Taken together, the effects of age on paths  $b$  and  $c'$  offset each other and  
270 resulted in an absence of accelerated aging in schizophrenia patients (Thuairé et al., 2020).  
271 Figure S2 shows that the direct effect of schizophrenia on updating is more negative with  
272 advancing years, whereas the indirect effect is less negative with age.

273

274 *Moderation by age of the mediation by speed of the group effect on inhibition:*

275 The analysis failed to show any moderation effect of age on paths  $b$  ( $B = .005, p = .237$ ) and  $c'$   
276 ( $B = -.006, p = .403$ ). Thus, the mediation by PS of the effect of schizophrenia on inhibition is  
277 not moderated by age.

278

279 *Moderation by age of the mediation by speed of the group effect on access:*

280 PROCESS analysis revealed a significant moderation effect on path  $c'$  ( $B = -.016, p = .045$ ).  
281 Thus, as shown in Figure S3, age moderated the direct effect of schizophrenia on access in a  
282 way that slowed the increase in schizophrenia patients' access performance with age.

283

284 **Discussion:**

285 The first aim of this study was to test the mediating role of PS on the effect of schizophrenia  
286 with respect to the four specific EFs, namely shifting, updating, inhibition and access. The  
287 second aim was to determine how age affected this mediation as a function of the four specific  
288 EFs.

289 Concerning the first goal, our results confirm the widely observed cognitive slowing in  
290 schizophrenia (Dickinson et al., 2007; Leeson et al., 2010; Mesholam-Gately et al., 2009; Neill  
291 & Rossell, 2013; Ojeda et al., 2012; Savla et al., 2011) and the effect of PS on EFs (Rose et al.,  
292 2011; Salthouse et al., 1998). Moreover, in accordance with the hypothesis that improving PS  
293 should bring widespread benefits in other cognitive functions (Cassetta & Goghari, 2016), PS  
294 mediates the effect of schizophrenia on EFs (Neill & Rossell, 2013; Ojeda et al., 2012; Savla et  
295 al., 2011). This result is consistent with Salthouse's Processing Speed Theory (Salthouse, 1996)  
296 and suggests PS should be efficient at successfully executing simple cognitive operations and  
297 keeping the result available for more complex operations such as cognitive strategies. Thus,  
298 fast processing may help to bear in mind current rules for shifting tasks, to switch faster between  
299 these rules, to update memory faster so that materials are not forgotten, to inhibit prepotent  
300 responses faster in order to activate an alternative response, and to activate and use efficient  
301 strategies to access memory.

302 With respect more specifically to mediation strength, shifting seems to be the specific EF  
303 mediated mainly by PS as it is the only one that showed significant total and indirect effects  
304 and no direct effect. The effect of schizophrenia on shifting is thus almost entirely the  
305 consequence of cognitive slowing. These results are in line with those of other studies which  
306 assessed shifting with the Wisconsin Card Sorting Test (Ojeda et al., 2012) or D-KEFS (Neill  
307 & Rossell, 2013; Savla et al., 2011). Our results also indicate that updating and access showed  
308 the most important total effect of schizophrenia, and both the direct and indirect effect remained  
309 significant, indicating that PS mediated most of the effect of schizophrenia on these EFs.

310 Finally, the mediation effect of schizophrenia on inhibition through PS is more complicated  
311 insofar as the total effect was not significant. According to Haye's Framework and contrary to  
312 Baron and Kenny's method (Baron & Kenny, 1986), a significant total effect is not required to  
313 test for mediation. More precisely, our result seems to be due to the opposite signs of the direct  
314 and indirect effects (Hayes, 2018). Thus, schizophrenia would seem to have a weak (and non-  
315 significant) positive direct effect (which is in keeping with both Baron and Kenny's and Haye's  
316 methods) on inhibition and a stronger negative indirect effect through PS. As the total effect is  
317 the sum of both direct and indirect effects (Hayes, 2018), the result is a non-significant total  
318 effect. This result warrants further research, but it is possible to speculate that if schizophrenia  
319 patients were not cognitively slowed their performances would be similar to comparison  
320 participants and even slightly better. Nevertheless, our results are in keeping with those  
321 observed with the D-KEFS in showing that PS contributed significantly to inhibition (Neill &  
322 Rossell, 2013; Savla et al., 2011).

323 The second aim was to determine whether age could be a moderator of this mediation effect as  
324 a function of the four specific EFs. Our main finding is that age moderated the mediation on  
325 three out of the four EFs, namely shifting, access and updating, albeit in different ways.  
326 According to a previous study (Thuaire et al., 2020) which showed that with respect to shifting  
327 and access schizophrenia patients were more affected by age than comparison participants, we  
328 postulated that the mediation effect on these EFs would be moderated by age. Our results  
329 supported this hypothesis and contributed to furthering knowledge about how age affects these  
330 functions in schizophrenia. Thus, the effect of PS on shifting was greater in older participants,  
331 suggesting that, compared with slower participants, faster participants may benefit from age as  
332 regards shifting. Yet, schizophrenia patients whose PS was severely impaired saw their shifting  
333 performance decline with age compared to healthy subjects, a result interpreted as accelerated  
334 aging (Thuaire et al., 2020).

335 With regard to access, the influence of age concerned the direct effect of schizophrenia and, as  
336 such, was independent from PS. More specifically, our results suggested that for comparison  
337 participants age was associated with an increase in access performance through the direct path,  
338 but that this was not the case for schizophrenia patients. The suggestion is therefore that it was  
339 the superior knowledge of vocabulary typical of healthy older adults (Fisk & Sharp, 2004)  
340 which was responsible for this increase in performance in the direct path. Moreover, where both  
341 groups were concerned, age affected the indirect path in the same way, namely through a  
342 slowing of processing which in turn reduced access performance. It is our suggestion that the  
343 two paths offset each other out for comparison participants, resulting in the absence of age  
344 effects (Fisk & Sharp, 2004), whereas for schizophrenia patients the direct path does not  
345 compensate for the indirect path. This interpretation of our results is in keeping with studies  
346 showing greater age-related decline in verbal fluency in schizophrenia patients (Kosmidis et al.,  
347 2005; Thuairé et al., 2020). It is therefore possible that schizophrenia patients did not improve  
348 their vocabulary with aging as much as comparison participants, or that they failed to use  
349 effective strategies in both fluency tasks.

350 Surprisingly, and contrary to our hypothesis, mediation of the effect of schizophrenia on  
351 updating by PS was also moderated by age. However, an examination of the direct and indirect  
352 effects indicated that moderation of these effects had opposite signs and thus resulted in the  
353 absence of accelerated aging with respect to updating (Thuairé et al., 2020). More precisely,  
354 moderation of the direct effect showed that schizophrenia patients were more impaired in terms  
355 of updating as they got older. Conversely, moderation of the indirect effect indicated that the  
356 influence of PS on updating decreased with age. As schizophrenia patients' PS was slower, they  
357 were less affected by age on this path, which offset the effect of the direct path. These results  
358 suggest that older participants relied less on PS to complete these updating tasks than their  
359 younger counterparts. We presume they tried to compensate for their cognitive slowing by



360 relying more on other processes such as working memory capacity or cognitive strategies, even  
361 if that was not enough for them to match the performance of younger participants (Thuaire et  
362 al., 2020). Such assumptions are in line with a meta-analysis of neuroimaging studies (Turner  
363 & Spreng, 2012), which showed that during an updating task older participants increased their  
364 recruitment of brain areas associated with learning and acquisition of cognitive strategies and  
365 cognitive control in working memory.

366 Finally, in keeping with our hypothesis and the fact that schizophrenia patients failed to show  
367 accelerated aging on inhibition (Thuaire et al., 2020), the mediation effect on this specific EF  
368 was not moderated by age.

369 These results suggest that PS should be assessed routinely during therapeutic follow-up and  
370 before including a patient in a remediation program. First, PS tasks are easy to administer and  
371 tap a central feature of the deficits in schizophrenia (Dickinson et al., 2007; González-Blanch  
372 et al., 2011). Second, since PS mediates EFs which are linked in turn to functional competences  
373 (Harvey et al., 1999; Kalache et al., 2015), evaluating it may help to target other functions for  
374 investigation and third, aging may have different effects on patients' cognition depending on  
375 their PS. Specifically, lowest performance patients may show a major deterioration in shifting  
376 performance but relatively spared updating performance.

377 Moreover, our results also show the importance of the choice of pharmacological treatment.  
378 Long-term benzodiazepine use seems to have negative effects on several areas of cognition,  
379 including PS, even after withdrawal (Crowe & Stranks, 2018), and so it should be prescribed  
380 with caution. Concerning the treatment of depression, which is a comorbidity of schizophrenia,  
381 a meta-analysis showed that selective serotonin reuptake inhibitors had greater positive effects  
382 on cognition in depressed patients than the other classes of antidepressants (Prado et al., 2018).  
383 This result should be confirmed with further researches and tested in schizophrenia because it  
384 represents a possible area for improving patients' cognition. In any case, pharmacological

385 treatment should be chosen and monitored so as to minimize neurocognitive side-effects, which  
386 may already be compromised by the disease process itself.

387 A potential implication of our results is that cognitive remediation programs should concentrate  
388 more on PS. Remediation programs targeting PS seem to be efficient (Garrido et al., 2013;  
389 Grynszpan et al., 2011; Lindenmayer et al., 2008; McGurk et al., 2007; Sartory et al., 2005;  
390 Vita et al., 2011). Thus, in light of our results showing that PS seems to underlie EFs, it is  
391 possible that increasing patients' PS would improve executive functioning (Rodríguez-sánchez  
392 et al., 2007).

393 This research has a number of strengths and limitations. First of all, EFs were assessed  
394 according to a validated model (Fisk & Sharp, 2004; Miyake et al., 2000) which depicts the  
395 diversity of EFs. Thus, our results lend further weight to arguments in favor of using specific  
396 models of executive functioning to study schizophrenia (Thuairé et al., 2020) insofar as we  
397 demonstrated how age affects the specific EFs differently through PS. Then, despite the  
398 numerous studies suggesting an underlying role for PS in the executive deficit in schizophrenia  
399 (Dickinson et al., 2007; Neill & Rossell, 2013; Ojeda et al., 2012; Raffard & Bayard, 2012;  
400 Rodríguez-sánchez et al., 2007; Savla et al., 2011), this article is the first to test this mediation  
401 with an appropriate statistical analysis. Moreover, patients and comparison subjects were  
402 rigorously paired, one by one, for gender, age and educational status. A recent meta-analysis  
403 (Fioravanti et al., 2012) indicated that the imbalance in the number of cases, gender composition  
404 and age could artificially increase between group differences. However, we were unable to  
405 control former patients' medication or to clarify the long-term effects of medication on  
406 cognitive functioning. This may be a recurrent problem with cross-sectional studies on  
407 schizophrenia aging (Suzuki et al., 2011). Nonetheless, patients were treated in accordance with  
408 the guidelines for biological treatment of schizophrenia published by the World Federation of  
409 Societies of Biological Psychiatry (Hasan et al., 2012, 2013). They received stable doses of

410 antipsychotics at least four weeks before inclusion and throughout the study, and most of the  
411 patients were administered only one antipsychotic which, presumably, would not cause  
412 excessive cognitive deficit. Moreover, pharmaceutical research is making constant progress, and  
413 differences in treatments between younger and older patients not only affect current patients  
414 but will probably continue in the future too. The life expectancy gap between schizophrenia  
415 patients and the general population (E. E. Lee et al., 2018) makes it difficult to recruit patients  
416 over the age of 70, with the result that comparison participants were not as old as typically  
417 found in healthy aging studies. However, only longitudinal designs could overcome this  
418 limitation by keeping age pairing. Another recurrent limitation is that there is no pure measure  
419 of EFs or PS, and even symbol coding requires memory and executive functioning (Knowles et  
420 al., 2015). To reduce these biases, we aggregated two tasks for each function, and PS tasks were  
421 administered for 30 seconds to avoid the use of strategies or memory to perform them.  
422 However, it should be borne in mind that these cognitive processes are intrinsically linked, and  
423 it is still possible that, in combination with the model we tested, where PS mediates EFs, there  
424 is also a model where EFs mediate some PS performance.

425 Another statistical limitation concerns the use of psychometric assessment based on theory  
426 rather than statistics. However, the tests we used have a strong theoretical framework, and as  
427 cognition in schizophrenia patients differs from that of the general population it did not seem  
428 appropriate to us to calculate a PCA.

429 In conclusion, this article is the first to show the mediation effect of PS on specific EFs with  
430 the help of a recent method that can be used to test the mediation directly (Hayes, 2018).  
431 Moreover, we showed that age affected the specific EFs through PS in different ways. These  
432 results have theoretical and clinical implications insofar as PS may explain various cognitive  
433 deficits in schizophrenia and should be a major target area for cognitive remediation. Several  
434 research studies have demonstrated the benefits of PS training (Garrido et al., 2013; Grynszpan

435 et al., 2011; Lindenmayer et al., 2008; McGurk et al., 2007; Sartory et al., 2005; Vita et al.,  
436 2011). However, there is a need for remediation programs that specifically target PS with a  
437 view to defining how speed improvement transfers to other abilities (Cassetta & Goghari,  
438 2016). Further research could test the hypothesis of a cascade model of cognition in  
439 schizophrenia, where PS impairment affects executive functioning, which, in turn, affects other  
440 cognitive processes, quality of life, and outcome. Another avenue for future research would be  
441 to complete our knowledge about relationships between cognitive processes in schizophrenia.  
442 For example, we could measure the contribution of attention, some components of which are  
443 impaired in schizophrenia. Indeed, top-down control of selective attention would appear to be  
444 impaired in schizophrenia, but not bottom-up control (Gold et al., 2018). Lastly, our results give  
445 indications for adapting cognitive remediation to suit older schizophrenia patients (Wykes et  
446 al., 2009) given that aging has a direct and stronger effect on updating and access in  
447 schizophrenia. However, there is no increased effect of age in patients with regards to inhibition  
448 and shifting, except through PS for the latter.

449

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461

462

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757 Table 1. Demographic characteristics of patients with schizophrenia and comparison



758 participants (standard deviations shown in brackets).

	Schizophrenia patients n=62	Comparison participants n=62	<i>t</i> -test	<i>p</i> value
Men/women	35/27	35/27		
Age (years)	46.4 (15.7)	46.7 (15.6)	0.1	<i>ns</i>
Level of education	11.3 (2.9)	11.5 (2.7)	0.3	<i>ns</i>
PANSS total	68.8 (18.8)			
Positive score	14.5 (5.1)			
Negative score	18.5 (7.4)			
General psychopathology	33.9 (9.4)			
HADS A	7.8 (3.8)	5.6 (3.4)	3.4	<.001
HADS D	6.4 (3.3)	3.8 (2.9)	4.8	<.001
Verbal IQ	86.6 (15.6)	99.2 (15.5)	4.5	<.001

759  
760 *Notes.* PANSS= Positive And Negative Symptom Scale; HADS= Hospital Anxiety and Depression Scale; IQ= Intelligence  
761 Quotient.

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

	Schizophrenia patients	Comparison participants
Shifting	-.302 (.844)	.302 (.414)
Updating	-.404 (.810)	.404 (.661)
Inhibition	-.058 (.876)	.058 (.600)
Access	-.481 (.886)	.481 (.666)
Speed	-.553 (.891)	.553 (.679)

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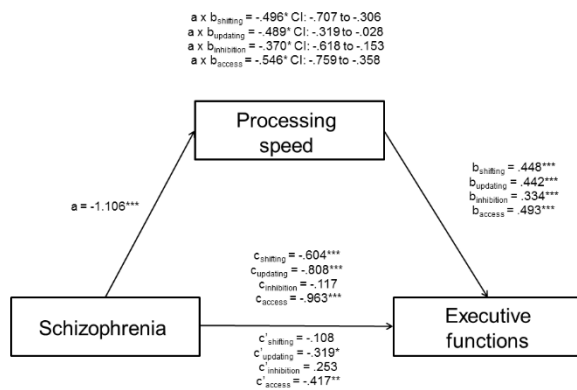
772 Table S1. Correlations between all study variables.

	2.	3.	4.	5.	6.	7.
1. Group	-.009	-.416 ***	-.483 ***	-.078	-.527 ***	-.576 ***
2. Age		-.272 **	-.290 **	-.473 ***	-.131	-.465 ***
3. Shifting			.477 ***	.394 ***	.447 ***	.636 ***
4. Updating				.366 ***	.604 ***	.617 ***
5. Inhibition					.299 ***	.332 ***
6. Access						.650 ***
7. Processing speed						

773 Note. \*\*  $p < .01$ . \*\*\*  $p < .001$ .

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775 Figure 1: Mediation model for the direct and indirect effects of schizophrenia on the four  
776 specific executive functions through processing speed. Numbers associated with  $a$ ,  $b$ ,  $c$ ,  $c'$  and  
777  $a \times b$  are unstandardized regression coefficients. \*  $p < .05$ . \*\*  $p < .01$ . \*\*\*  $p < .001$ . CI = 95%  
778 bias-corrected bootstrap confidence interval.



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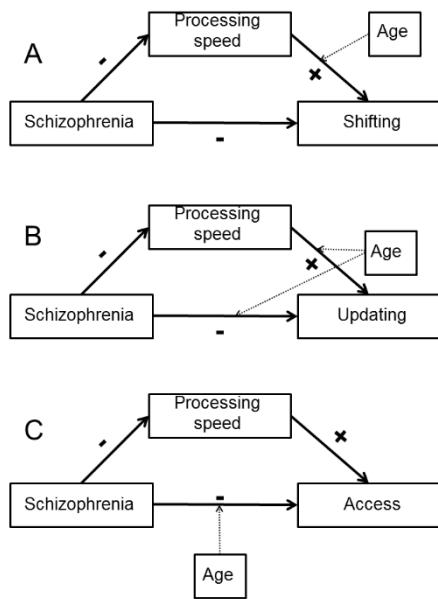
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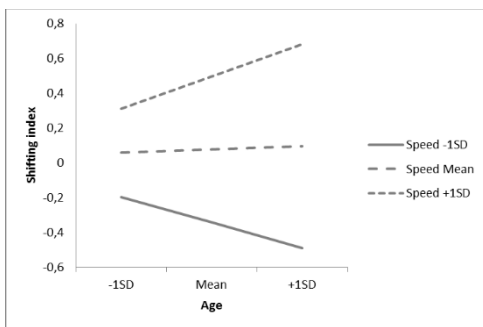
787 Figure 2: Representation of the mediation of the effect of schizophrenia on executive  
788 functions through processing speed moderated by age for shifting (A), updating (B) and

789 access (C).



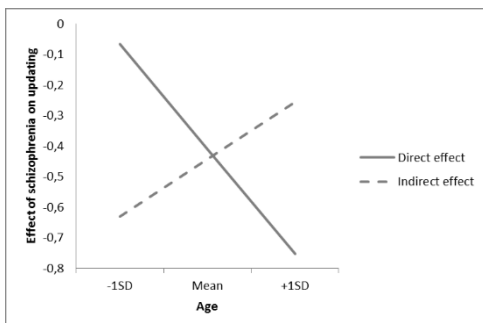
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791 Figure S1: Moderation of the effect of processing speed on shifting by age.



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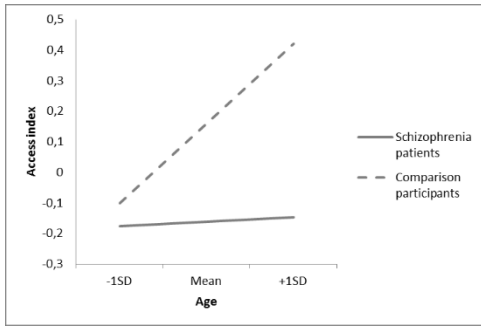
793 Figure S2: Direct and indirect effects of schizophrenia on updating as a function of participants'  
794 age.



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796 Figure S3: Moderation of the direct effect of schizophrenia on access by age.

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