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1 **TOOL USE DISORDERS IN NEURODEGENERATIVE DISEASES:**
2 **ROLES OF SEMANTIC MEMORY AND TECHNICAL**
3 **REASONING**

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25 **ABSTRACT**

26 In the field of apraxia, it has been suggested that the ability to use tools and objects in
27 daily life depends not only on semantic knowledge about tool function and context of use but
28 also on technical reasoning about mechanical properties of tools and objects. The aim of the
29 present work was to assess tool use abilities regarding these hypotheses in patients with
30 neurodegenerative diseases and reduced autonomy. Performance of patients with Alzheimer's
31 disease (n = 31), semantic dementia (n = 16) and corticobasal syndrome (n = 7) was compared
32 to that of healthy control participants (n = 31) in familiar tool use tasks, functional/contextual
33 associations and mechanical problem solving. A conversion method was applied to data in
34 order to avoid ceiling effects. Tool use disorders were found in all patient groups but the
35 underlying reasons were different. Patients with semantic dementia had difficulties in
36 imagining and selecting familiar tools due to the semantic loss but they performed in normal
37 range in mechanical problem solving tasks. Interestingly, they performed better with only one
38 tool and its corresponding object, which is interpreted as a partial compensation of semantic
39 loss by spared technical reasoning. Patients with corticobasal syndrome exhibited the reverse
40 pattern, that is, mechanical problem solving deficits without semantic loss. However,
41 additional qualitative research is needed to disentangle the relative contributions of motor and
42 technical reasoning deficits to this pattern. Both of these profiles were found in patients with
43 Alzheimer's disease. For all that, these patients did not commit the same errors as stroke
44 patients with left brain-damage documented in previous works. Several hypotheses are
45 proposed to account for the specificity of tool use disorders in neurodegenerative diseases,
46 and recommendations are provided to caregivers.

47 **KEYWORDS**

48 *Keywords: Alzheimer's disease, semantic dementia, corticobasal degeneration, mechanical*
49 *problem-solving, apraxia.*

50

ACCEPTED MANUSCRIPT

51 **PRINTING**

52 We recommend printing in black-and-white.

ACCEPTED MANUSCRIPT

53 **ABBREVIATIONS**

- 54 - AD: Alzheimer’s disease (as a group).
55 - BEC: “Batterie d’Evaluation Cognitive” (a French neuropsychological battery)
56 - CBS: Corticobasal syndrome
57 - FAB: Frontal Assessment Battery
58 - FCA: Functional and Contextual Associations
59 - HC: Healthy controls (as a group)
60 - MMSE: Mini Mental State Examination
61 - MPS.C: Mechanical Problem Solving (choice condition)
62 - MPS.NC: Mechanical Problem Solving (no choice condition)
63 - RTU.C: Real Tool Use (choice condition)
64 - RTU.NC: Real Tool Use (no choice condition)
65 - SD: Semantic dementia (as a group)
66 - STU: Single Tool Use

67

68 I. INTRODUCTION

69 1. 1. AIMS OF THE PRESENT STUDY

70 It is known that difficulties in using everyday tools and objects are a core manifestation
71 of apraxia (Baumard, Osiurak, Lesourd, & Le Gall, 2014; Bienkiewicz, Brandi, Goldenberg,
72 Hughes, & Hermsdörfer, 2014; Goldenberg, 2009; Heilman, Maher, Greenwald, & Rothi,
73 1997). It is also well-known that patients with dementia have difficulties in performing usual
74 activities as well as in solving complex or novel problems (McKhann et al., 2011).
75 Nevertheless, only very few studies have investigated tool use abilities in neurodegenerative
76 diseases (see for example Lesourd et al., 2013), perhaps because the cognitive processes
77 underlying tool use are still under debate (Buxbaum, Shapiro, & Coslett, 2015; Osiurak &
78 Badets, 2016; Osiurak, Jarry, & Le Gall, 2010, 2011; Osiurak & Le Gall, 2014). In view of
79 recent models of apraxia, normal tool use may depend on two complementary mechanisms,
80 that is, semantic knowledge about tool function and context of use (Osiurak, 2014; Rothi,
81 Ochipa, & Heilman, 1991, 1997; Roy, 1996; Roy & Square, 1985), and technical reasoning
82 about physical properties of tools and objects (Osiurak et al., 2010, 2011; Reynaud, Lesourd,
83 Navarro, & Osiurak, 2016; for a similar view, see Goldenberg & Hagmann, 1998). In light of
84 these hypotheses, the aim of the present study was to describe tool use disorders in dementia
85 through a differential approach, in Alzheimer's disease, semantic dementia and corticobasal
86 syndrome.

87 1. 2. THEORETICAL BACKGROUND

88 1.2.1. DEMENTIA SUBTYPES

89 Dementia is defined as a progressive decline of memory, reasoning, judgment,
90 visuospatial skills, language and/or social behavior, interfering with usual activities and hence
91 reducing autonomy (McKhann et al., 2011). Logically, tool use disorders should be observed

92 in all-cause dementia but the underlying cognitive impairments are likely to be etiology-
93 specific since the pattern of brain atrophy and the expected neuropsychological profile vary
94 according to diagnosis. Semantic dementia is associated with circumscribed atrophy of the
95 ventral temporal lobes. It is characterized by a loss of knowledge observed in language (i.e.,
96 fluent but empty speech, loss of word meaning, semantic paraphasias) and/or perception (i.e.,
97 prosopagnosia, impaired recognition of objects identity or function) contrasting with normal
98 language processing (i.e., repetition, reading) and perception (i.e., perceptual matching,
99 picture reproduction; Gorno-Tempini et al., 2011; Neary et al., 1998). Corticobasal
100 degeneration is characterized by brain atrophy in the basal ganglia and in frontal and parietal
101 brain regions. It is associated with asymmetric limb rigidity, akinesia, dystonia and/or
102 myoclonus, as well as with orobuccal or limb apraxia (i.e., ideomotor and/or limb-kinetic
103 apraxia), cortical sensory deficit and/or alien limb phenomenon, but additional cognitive
104 impairments are exclusion criteria (Armstrong et al., 2013; Litvan et al., 1997). The clinical
105 diagnosis of Alzheimer's disease requires either episodic memory disorders (i.e., amnesic
106 presentation) or language, visuospatial or executive dysfunction (i.e., non-amnesic
107 presentation; McKhann et al., 2011). Lesions are typically observed in the hippocampal
108 region but they may also extend to frontal and parietal lobes.

109 According to Felician, Ceccaldi, Didic, Thinus-Blanc and Poncet (2003), cortical
110 neurodegenerative diseases are well-suited models for testing cognitive-based hypotheses, for
111 three reasons. First, lesions are relatively circumscribed at early stages of the disease. Second,
112 in most cases the progression of cognitive impairments is stereotyped and sequential. Third,
113 slowly progressive diseases may result in more stable functional reorganization than non-
114 progressive lesions. Thus, it is appropriate to search for dissociations between semantic loss
115 and problem solving deficits in neurodegenerative diseases.

116 1.2.2. THE SEMANTIC MEMORY HYPOTHESIS

117 According to cognitive models of apraxia (Rothi et al., 1991, 1997; Roy, 1996; Roy &
118 Square, 1985), tool use depends on explicit semantic knowledge about tool-object usual
119 relationships (e.g., a hammer goes with a nail) and tool function (e.g., a hammer and a mallet
120 share the same purpose). Notice that we shall use the terms "tool" and "object" to refer to the
121 implement performing the action (e.g., screwdriver) and the recipient of the action (e.g.,
122 screw), respectively. Likewise, semantic memory may inform individuals about where to find
123 tools if not present in the visual field (e.g., knowing that a hammer can be found in a
124 workshop; see Osiurak, 2014; Osiurak et al., 2010). Loss of this type of knowledge causes
125 conceptual apraxia, which prevents patients from either selecting relevant tools among
126 distractors in multiple object tasks (Ochipa, Rothi, & Heilman, 1992), choosing among
127 several pictures the one that shares common features with a target picture (i.e., functional
128 association) or performing tool-related gestures in the absence of objects, as in single tool use
129 (to be described in section 2. Materials and methods). Semantic knowledge about tool function
130 and context of use is commonly associated to the ventral, temporal lobes (Goldenberg &
131 Spatt, 2009), a brain region that is early impaired in the course of Alzheimer's disease (Braak
132 & Braak, 1995, 1997) and semantic dementia (Galton et al., 2001). In comparison, temporal
133 lobe lesions are not typical of corticobasal degeneration (see for example Boeve, Lang, &
134 Litvan, 2003), even though there is a high heterogeneity as regards the distribution of cerebral
135 cortical lesions in this disease (Armstrong, Cairns, & Lantos, 1999; Tsuchiya, Ikeda,
136 Uchihara, Oda, & Shimada, 1997).

137 As a matter of fact, conceptual apraxia has been found in patients with Alzheimer's
138 disease (Crutch, Rossor, & Warrington, 2007; Derouesné, Lagha-Pierucci, Thibault, Baudoin-
139 Madec, & Lacomblez, 2000; Ochipa et al., 1992; Okazaki, Kasai, Meguro, Yamaguchi, &
140 Ishii, 2009; Rapcsak, Crosswell, & Rubens, 1989) and semantic dementia (Hodges, Bozeat,
141 Lambon-Ralph, Patterson, & Spatt, 2000; Hodges, Spatt, & Patterson, 1999; Moreaud,

142 Charnallet, & Pellat, 1998). Interestingly, some patients may perform better with only one tool
143 and its corresponding object (Bozeat, Lambon-Ralph, Patterson, & Hodges, 2002; Dumont,
144 Ska, & Joannette, 2000; Ochipa *et al.*, 1992) even though there is no consensus on it
145 (Derouesné *et al.*, 2000). In corticobasal degeneration, both single tool use and intransitive
146 communicative gestures have been found to be impaired (Buxbaum, Kyle, Grossman, &
147 Coslett, 2007). This may be accounted for by elementary motor, sensitive and proprioceptive
148 disorders (Graham, Zeman, Young, Patterson, & Hodges, 1999) rather than by loss of
149 conceptual knowledge since the latter is not part of the expected neuropsychological profile
150 (Armstrong *et al.*, 2013; Pillon *et al.*, 1995).

151 For all that, a growing amount of evidence suggests that tool-related knowledge is
152 neither necessary nor sufficient to support tool use (Buxbaum and Saffran, 2002; Buxbaum,
153 Schwartz, & Carew, 1997; Hodges *et al.*, 2000; Osiurak *et al.*, 2008), which implies that non-
154 semantic factors may compensate for semantic loss (Silveri & Ciccarelli, 2009).

155 1.2.3. THE TECHNICAL REASONING HYPOTHESIS

156 According to the technical reasoning hypothesis (Gagnepain, 1990; Le Gall, 1998;
157 Osiurak *et al.*, 2010, 2011; for a similar view, see Goldenberg, 2009; Goldenberg & Hagmann,
158 1998; Goldenberg & Spatt, 2009; Hartmann, Daumüller, Goldenberg, & Hermsdörfer, 2005),
159 the use of both familiar and novel tools is made possible by reasoning on the relative,
160 mechanical properties of tools and objects (e.g., copper is “resistant” when applied to
161 sandstone but “breakable” when compared to diamond). This cognitive mechanism is likely to
162 rely on the activity of the left inferior parietal lobe (Goldenberg, 2009; Orban & Caruana,
163 2014; Reynaud *et al.*, 2016) and can be impaired independently from the presence of
164 dysexecutive syndrome (Goldenberg, Hartmann-Schmid, Sürer, Daumüller, & Hermsdörfer,
165 2007). Parietal lobes are generally spared in semantic dementia (Mummery *et al.*, 2000) but

166 atrophied in Alzheimer's disease (Braak & Braak, 1991; Foundas, Leonard, Mahoney, Agee,
167 & Heilman, 1997) and corticobasal degeneration (Litvan et al., 1997).

168 In a clinical setting, technical reasoning is thought to be involved in real tool use but can
169 be more specifically assessed through mechanical problem solving tasks involving reasoning
170 on the physical properties of novel tools and objects (Goldenberg & Hagmann, 1998; Heilman
171 et al., 1997; Jarry et al., 2013). This ability has been rarely investigated in corticobasal
172 degeneration. Spatt, Bak, Bozeat, Patterson and Hodges (2002) described five patients who
173 met difficulties in novel tool selection and use. Likewise, patients with Alzheimer's disease
174 seem to have deficits in unconventional tool use (Derouesné et al., 2000) and mechanical
175 problem solving (Ochipa et al., 1992). Conversely, patients with semantic dementia may
176 exhibit dissociation between impaired familiar tool use and spared mechanical problem
177 solving skills (Hodges et al., 1999, 2000). Therefore, spared technical reasoning might
178 compensate to some extent for semantic memory loss (as previously proposed by Hodges et
179 al., 1999, 2002) but there is no extensive differential study on this topic and, unfortunately,
180 existing data cannot be reinterpreted in that way due to frequent ceiling effects. In order to
181 prevent this bias, we normalized data by combining raw efficiency scores and completion
182 time (see section 2.4. General scoring system).

183 *1.2.4. PREDICTIONS*

184 The semantic memory hypothesis predicts that defective semantic knowledge about tool
185 use (as demonstrated by deficits in Functional and Contextual Associations; see Section 2.2.3.
186 Experimental protocol) should prevent patients from demonstrating the use of tools presented
187 in isolation (i.e., Single Tool Use) because they should not be able to imagine neither the
188 object which is usually associated with the tool, nor the typical action to be performed with it.
189 Likewise, selection of a tool among distractors (i.e., Real Tool Use, Choice condition) is
190 expected to be impaired seeing that different tools may offer similar technical potentials. For

191 example, scissors, a knife and a screwdriver are all relevant to perform the action [driving a
192 screw into a wooden board] but everyone is used to select the screwdriver because it is more
193 frequent in our culture. In case of semantic loss, non-canonical (but technically relevant) tools
194 might be selected. Said differently, there is no reason to select the screwdriver since the two
195 other tools are also technically relevant, meaning that all of the three tools have an equal
196 chance to be selected. In contrast, it can be predicted that using a tool with the corresponding
197 object (i.e., Real Tool Use, No-Choice condition) is easier because in that case, technical
198 reasoning alone might compensate the lack of knowledge about the tool and the object.
199 Furthermore, according to the semantic memory hypothesis, positive correlations are expected
200 between Functional/Contextual Associations, Single Tool Use and Real Tool Use.

201 According to the technical reasoning hypothesis, impaired technical reasoning (as
202 demonstrated by deficits in mechanical problem-solving tasks; see Section 2.2.3.
203 Experimental protocol) is expected to result in low performance in both Single Tool Use and
204 Real Tool Use (whether with or without choice). Indeed, the technical reasoning hypothesis
205 predicts consistent correlations between mechanical problem-solving and both of these
206 conditions, as previously found in patients with left brain-damage (Jarry et al., 2013). The
207 rationale is as follows. In case of isolated abnormal technical reasoning, patients may be able
208 to match pictures of a tool and its corresponding, usual object in some instances. However, in
209 presence of real tools and objects, selecting which technical potentials are relevant to perform
210 the action should be especially difficult. As a consequence both tool selection and tool
211 application deficit should be observed (tool application is defined as the efficient interaction
212 between a tool and an object), as it has been described in stroke patients (Goldenberg &
213 Hagmann, 1998). For example, patients may know that a screw and a screwdriver usually fit
214 together while being unable to analyze which tool, which part of the tool and which actions
215 are relevant to perform the expected action.

216 As mentioned above, patients with semantic dementia have lesions in the temporal lobes
217 and semantic memory deficit so the semantic memory hypothesis is expected to apply to this
218 group. Patients with corticobasal degeneration have lesions in the parietal lobes so the
219 technical reasoning hypothesis is expected to be true in this group. Patients with Alzheimer's
220 disease may have lesions in both of these brain regions so both predictions may be observed.
221 Considering that both semantic memory and technical reasoning may be involved in familiar
222 tool use, these patients may exhibit particularly severe tool use disorders.

223 II. MATERIALS AND METHODS

224 2.1. PARTICIPANTS

225 Four groups of French participants (Table 1) were exposed to the same fixed testing
226 procedure: three groups of patients with Alzheimer's disease (AD, $n = 31$), semantic dementia
227 (SD, $n = 16$) or corticobasal syndrome (CBS, $n = 7$), and a group of healthy control
228 participants (HC, $n = 31$). It should be noticed that the clinical diagnosis of corticobasal
229 syndrome may be associated with cytopathological changes of either Alzheimer's disease or
230 corticobasal degeneration depending on the presence of either memory impairments or
231 behavioral changes, respectively (Shelley, Hodges, Kipps, Xuereb, & Bak, 2009). In the CBS
232 group, five patients had normal cognitive functioning but two patients had memory, language,
233 visuoconstructive and executive dysfunction. In the absence of post-mortem confirmation, the
234 label "corticobasal syndrome" rather than "corticobasal degeneration" was considered to be
235 more rigorous. Patients from other groups did not exhibit corticobasal syndrome. All patients
236 were consecutively recruited from four neurological departments (Angers, Lyon, Rennes,
237 Grenoble). They lived at home and had no previous history of neurological or psychiatric
238 illnesses. The study was conducted in conformity with the Declaration of Helsinki and

239 approved by local ethical committee (Western Protection to Persons Committee II, n°
240 2012/32).

241 Participants were excluded in the following situations: severe dementia as disclosed by
242 a score ≤ 10 on the MMSE (Folstein, Folstein, & McHugh, 1975), rheumatologic condition,
243 mood disorders, medical treatment or comprehension impairment that could interfere with
244 performance. All patients underwent neurological examination and extensive
245 neuropsychological assessment. Cerebro-spinal fluid biomarkers were collected to confirm
246 diagnosis in most patients. Imaging data did not show evidence of cerebrovascular damage.
247 Patients with Alzheimer's disease fulfilled the criteria for diagnosis of probable Alzheimer's
248 disease (McKhann et al., 2011) and imaging demonstrated hippocampal atrophy with or
249 without background cerebral atrophy. The clinical diagnosis of semantic dementia required
250 progressive loss of meaning of words, objects and/or faces in the context of relatively spared
251 episodic memory, perceptual and language abilities (Gorno-Tempini et al., 2011; Neary et al.,
252 1998). Cortical atrophy and/or hypoperfusion circumscribed to (or at least predominant in) the
253 temporal polar regions were consistently observed. In both of these groups, vestibular,
254 cerebellar, sensitive, pyramidal and parkinsonian syndrome were dismissed. Corticobasal
255 syndrome was diagnosed in patients with a parkinsonian syndrome coupled with cortical signs
256 such as orobuccal, limb and/or limb-kinetic apraxia, sensory deficit, alien limb phenomena,
257 executive dysfunction or moderate visuospatial deficit (Armstrong et al., 2013; Litvan et al.,
258 1997). In this group, vestibular and cerebellar syndromes were dismissed. Imaging data
259 confirmed asymmetric atrophy in both frontoparietal cortical areas and basal ganglia.

260 The HC group was a control group for patients. It was matched with the AD group for
261 gender and age (Table 1). A Kruskal-Wallis rank sum test revealed significant age differences
262 ($H = 16.8$, $df = 3$, $p < .001$). Pairwise Wilcoxon comparisons with Holm's correction
263 confirmed that patients with semantic dementia were slightly younger than those with

264 Alzheimer's disease ($W = 406.0, p = .002$) and healthy controls ($W = 402.5, p .002$), which
265 makes sense because the age of onset is frequently earlier in semantic dementia than in
266 Alzheimer's disease (see for example Hodges, Patterson, Oxbury, & Funnell, 1992; Snowden
267 et al., 2001). No other age differences were significant. The educational level was
268 significantly lower in the Alzheimer group compared with other groups (Table 1) but no
269 correlation was found between this variable and experimental measures in healthy participants
270 (Spearman rank order correlations with Holm's correction for multiple tests, all $ps > .24$).

271 < Insert Table 1 about here >

272 2.2. NEUROPSYCHOLOGICAL TESTING

273 Neuropsychological data were collected in all participants with three standard tests:

274 (1) The Mini Mental State Examination (Folstein, Folstein, & McHugh, 1975);

275 (2) A French neuropsychological battery (the BEC 96 questionnaire, Signoret et al.,
276 1989) composed of eight subtests ordered as follows: working memory (i.e., saying the days
277 of the week in reverse order), orientation questions, general verbal reasoning (i.e., arithmetic
278 problem-solving, word-categorization, proverb comprehension), verbal fluency (i.e.,
279 providing as many animal names as possible in 2 minutes), visual recognition (i.e., 10-min
280 recall and recognition of six black and white depicted objects), verbal learning (i.e., three
281 immediate recalls of eight words), naming and visuo-constructive skills (i.e., copying two 3D
282 and 2D geometrical drawings). Maximum score per subtest is twelve (total score = 96) with
283 any score below nine indicating pathological performance according to French normative
284 data.

285 (3) A fast frontal assessment battery (FAB, Dubois, Slachevsky, Litvan, & Pillon, 2000)
286 which includes word-categorization, letter fluency, assessment of grasping, deferred imitation
287 of movement sequence and two conflict go-no-go tasks. Each subtest is scored on a 3-point

288 scale (total score = 18). Any score below fifteen demonstrates executive dysfunction
289 according to French normative data.

290 2.3. EXPERIMENTAL PROTOCOL

291 Very similar procedures have already been used in previous works (Goldenberg et al.,
292 2007; Jarry et al., 2013). Patients were allowed to use both hands in all experimental tasks,
293 which were administered in the following order.

294 2.3.1. SINGLE TOOL USE (STU)

295 Ten common tools (plus one corrected, practice item) were presented one at a time on a
296 vertical panel (Supplementary Fig. 1). Participants were asked to grasp the tool and to
297 demonstrate its typical use. The examiner did not name the tools. The time limit was set to 20
298 seconds per item. Performance was videotaped and rated on a 3-point scale (maximum = 20):
299 (2) the expected action was clearly recognizable and performed without hesitation; (1) the
300 gesture was recognizable but with hesitations or errors (i.e., spatiotemporal errors); (0)
301 unrecognizable gesture (i.e., content error). Two independent judges coded videos from 10
302 Alzheimer patients and 10 control participants who were not included in the HC group. Inter-
303 coders agreement was high for scores (Pearson's product moment correlation, $r = 0.95$, $p <$
304 $.001$) and completion time ($r = 0.82$, $p < .001$).

305 2.3.2. REAL TOOL USE (RTU)

306 Participants were asked to actually use ten tool-object pairs (Supplementary Fig. 1) plus
307 one practice pair. The examiner did not name tools, objects or actions to be done. There were
308 two versions of this test. In the Choice condition, participants were asked to select one of the
309 ten tools and to use it with the presented object. In the No-choice condition, the participant
310 was given only a tool/object pair. The time limit was set to 60 seconds per item in the Choice
311 condition and 30 seconds in the No-choice condition because the need to select tools
312 presumably called for additional cognitive processing. One point was given if the participant

313 produced the expected action with the expected tool (maximum = 10 in each condition). In
314 addition, in the Choice condition the number of unexpected tools removed from the panel by
315 the participant was summed up across all items.

316 2.3.3. MECHANICAL PROBLEM SOLVING (MPS)

317 This test assessed tool use abilities with novel tools and objects, that is, without
318 reference to semantic knowledge. Experimental materials included three transparent boxes
319 (one per item) and eight rods (Supplementary Fig. 2) that differed on material, length,
320 diameter, bendability and friability. Participants were asked to extract a red wooden target (a
321 cube or a bead) from each box using the rods. Each problem called for different mechanical
322 actions (e.g., pushing, pulling, levering) and could be solved in two stages but not by hand, by
323 chance or by random selection of the rods. A fourth box and one additional rod were used as a
324 practice item.

325 In the Choice condition, participants were presented with the eight rods and one box at a
326 time. They could use and combine as many rods as necessary although for each box, two rods
327 allowed solving the whole problem. Some other rods could be relevant depending on the
328 status of the problem. In the No-choice condition, participants were given only one relevant
329 rod. The time limit was set to 3 minutes per item in both conditions. Performance was rated
330 on a 4-point scale (maximum score = 9 for each condition): (3) The target is extracted from
331 the box within the time limit; (2) The participant goes beyond the first stage of the problem
332 (e.g., for box 1, he inserts a long rod into the “chimney” and pushed the cube so that it falls
333 into the box; see Supplementary Fig. 2); (1) The participant reaches the target with a rod but
334 he does not fulfill the first stage; (0) The participant does not reach the target with a rod.

335 2.3.4. FUNCTIONAL AND CONTEXTUAL ASSOCIATION (FCA)

336 Two tests were proposed to assess semantic knowledge about tools without effective
337 tool manipulation. In both tests, participants were asked to select among an array of four

338 pictures the one that best matched the picture of a tool (the same ten tools employed in tool
339 use tasks). In Functional Association, the matching criterion was the function of the tool (e.g.,
340 target = match; choice = *lighter*, pen, coffee maker, colander). In Contextual Association, the
341 criterion was its usual context of use (e.g., target = match; choice = *anniversary*, wedding,
342 Christmas day, baptism). There were ten items in each condition (plus two corrected, practice
343 items). Each correct answer given within 20 seconds was worth 1 point (maximum score =
344 20).

345 2.4. GENERAL SCORING SYSTEM

346 Ceiling effects are very frequent in the field of apraxia, whether in healthy participants,
347 in stroke patients or in patients with dementia (Baumard et al., 2014; Lesourd et al., 2013).
348 Yet, they can minimize the differences between groups so that data only indicate the presence
349 or absence of impairment but not its severity. In order to overcome such problems, we
350 adopted an original scoring procedure that is close to the one employed in the Wechsler Adult
351 Intelligence Scale (Wechsler, 1997). The method took three steps: (1) Completion time (i.e.,
352 the time period between the presentation of an item and the moment the participant obtained
353 the best possible score) was collected from videos in each item; (2) The 5th, 25th, 75th and 95th
354 percentile ranks were calculated for completion time for each item in the control group; (3)
355 Additional points were given to all participants depending on completion time
356 (Supplementary Table 1). This procedure was tested in a group of seventy-two healthy
357 participants before use in the present work, demonstrating that time-based scores were
358 normally distributed in all experimental tests (Supplementary Fig. 3).

359 Besides, processing speed was assessed in all participants using a paper-and-pencil
360 tracking task (Baddeley, 1996) so as to control for general cognitive slowing. Participants
361 were presented with a chain of 0.5-cm-square boxes forming an irregular path on a sheet of
362 paper. They were asked to draw a cross in each box in turn, following the path and working as

363 rapidly as possible. The score was the number of crosses made within a two-minute time
364 limit.

365 2.5. STATISTICAL ANALYSIS

366 Despite normal distribution of data, non-parametric tests were preferred because of
367 small sample sizes. We employed a three-step, non-Bayesian data analysis approach. First, we
368 examined between-group differences using Kruskal-Wallis tests and post-hoc Mann-Whitney
369 U-tests, and within-group differences using Wilcoxon tests. Second, the correlational structure
370 was explored with Spearman rank order correlations. Holm's correction for multiple tests was
371 applied. With the idea to infer general factors from experimental measures, we conducted a
372 principal component analysis with the active variables (i.e., variables used to infer
373 components) Mechanical Problem Solving (both conditions) and Functional/Contextual
374 Associations. Age, Educational level, Processing speed, Single Tool Use and Real Tool Use in
375 both conditions were included as additional quantitative variables and the factor GROUP as
376 an additional qualitative variable. Data were standardized so that all variables had the same
377 weight. Next, we examined correlations between dimensions, active variables and additional
378 variables. All analyses were performed with R statistical software. Third, single cases were
379 examined using a dedicated statistical method (Crawford & Garthwaite, 2002, 2005).

380 III. RESULTS

381 3.1. EFFECTS OF DEMOGRAPHIC DATA AND NEUROPSYCHOLOGICAL TESTING

382 No linear relationship was observed between age, educational level and experimental
383 measures in the control group (all $ps > .08$). Sixteen Alzheimer patients had mild cognitive
384 decline (MMSE 26-21; subgroup 1, mean score = 22.3/30, SD = 1.2/30) whereas fifteen had
385 moderate to severe decline (MMSE 20-11; subgroup 2, mean score = 18.0/30, SD = 2.3/30;
386 see Reisberg et al., 1982). Both groups obtained similar results in Real Tool Use, choice

387 condition (subgroup 1: mean score = 28.4 %, SD = 13.3 %; subgroup 2: mean score = 21.4 %,
388 SD = 13.3 %; $U = 158.5$, $p = .13$) and even subgroup 1 was significantly impaired when
389 compared to healthy controls (mean MMSE score = 27.2/30, SD = 1.7/30; mean Real Tool
390 Use score = 60.6 %, SD = 12.0 %; $U = 453.5$, $p < .001$).

391 Results of the Frontal Assessment Battery yielded comparable results in patients with
392 Alzheimer's disease (mean score = 71.1 %, SD = 12.8 %), semantic dementia (mean score =
393 75.0 %, SD = 12.2 %, 3 missing values due to comprehension deficits) and corticobasal
394 syndrome (mean score = 67.2 %, SD = 22.8 %; $H = 0.94$, $df = 2$, $p = .62$).

395 With respect to the BEC 96 questionnaire, significant general cognitive impairment was
396 observed in comparison with healthy controls (mean score = 91.3 %, SD = 5.5 %), in
397 Alzheimer's disease (mean score = 70.3 %, SD = 9.7 %; $U = 939.0$, $p < .001$), semantic
398 dementia (mean score = 70.8 %, SD = 9.4 %; $U = 392.0$, $p < .001$) and corticobasal syndrome
399 (mean score = 79.6 %, SD = 14.3 %; $U = 172.0$, $p = .017$). As shown in Figure 1, Alzheimer
400 patients had mainly severe memory and orientation disorders. In contrast, patients with
401 semantic dementia performed worse in tasks assessing language and semantic memory but
402 they could answer orientation questions. Patients with corticobasal syndrome had
403 constructional deficits due to motor disorders but other dimensions were spared in most
404 patients.

405 Finally, in the tracking task, Alzheimer patients (mean score = 74.9, SD = 34.0) were
406 slower than healthy controls (mean score = 107.6, SD = 37.2; $U = 629.5$, $p < .001$) while this
407 was not the case for patients with semantic dementia (mean score = 85.9, SD = 39.6; $U =$
408 141.5 , $p = .22$). Missing data for three out of seven cases (due to motor deficits) did not allow
409 reliable comparison as regards patients with corticobasal syndrome but they appeared clearly

410 slower than healthy controls (mean score = 59.0, SD = 33.1). In the healthy control group, no
411 correlation was found between processing speed and experimental measures (all $ps > .26$).

412 < Insert Figure 1 about here >

413 3.2. COMPARISONS BETWEEN GROUPS

414 As shown in Figure 2, all patient groups exhibited tool use disorders, whether in Single
415 Tool Use or Real Tool Use. Compared to healthy controls, patients with semantic dementia
416 had difficulties in Functional/Contextual Associations but not in Mechanical Problem Solving.
417 The reverse pattern was observed in patients with corticobasal syndrome. On average, healthy
418 controls selected 0.7 irrelevant tools in the Real Tool Use task (range = 0-3) against 1.8 in
419 Alzheimer patients (range = 0-6; $U = 660.5$, $p = .04$) and 3.1 in patients with semantic
420 dementia (range = 0-13; $U = 367.5$, $p = .027$); the difference was not significant as regards
421 corticobasal syndrome (mean = 0.7, range = 0-2; $U = 113.0$, $p = .92$). Besides, SD patients
422 scored significantly higher than AD patients in Mechanical Problem Solving ($U = 384.5$, $p =$
423 $.011$) but tended to have lower scores than other patients groups in Functional/Contextual
424 Associations (both $ps = .084$). Other differences were not significant (all $ps > .08$).

425 In Real Tool Use (Choice), all patient groups had lower performance than healthy
426 controls (all $ps < .022$). In the No-choice condition, the difference was significant only in
427 CBS and AD patients (both $ps < .011$) but not in SD patients despite a tendency toward
428 significance ($W = 138.5$, $p = .057$). In the Choice condition of Mechanical Problem Solving,
429 AD and CBS patients performed worse than healthy controls (both $ps < .02$), contrary to SD
430 patients ($W = 167.0$, $p = .20$). The same pattern was observed in the No-choice condition.

431 < Insert Figure 2 about here >

432 3.3. COMPARISONS WITHIN GROUPS

433 Within-subject differences were calculated in order to highlight the following effects: 1)
434 presence/absence of objects (i.e., Single Tool Use versus Real Tool Use, No-choice
435 condition); 2) choice versus no-choice conditions, in both Real Tool Use and Mechanical
436 Problem Solving; 3) familiarity versus novelty of tools and objects (i.e., Real Tool Use versus
437 Mechanical Problem Solving). To this end, we used the following formula: [(Task 2 – Task 1)
438 / Task 1]. With this method, each case was compared to himself or herself. Results are
439 displayed in Figure 3. Within-group comparisons were performed on composite scores (with
440 Wilcoxon tests) in order to assess simple task effects, then between-group comparisons were
441 performed on this difference (with Mann-Whitney U-tests) in order to determine whether task
442 effects were specific to a certain group.

443 The choice/no-choice difference was significantly higher in SD patients than in CBS
444 patients ($U = 107.5, p = .002$) and healthy controls ($U = 467.0, p < .001$) and there was a trend
445 toward a significant difference when comparing SD and AD patients ($U = 343.0, p = .067$).
446 Likewise, this difference was higher in the AD group than in the CBS group ($U = 189.5, p =$
447 $.007$). As regards Mechanical Problem Solving, the mean improvement between choice and
448 no-choice conditions was virtually the same in all groups (Kruskal-Wallis test, $p = .31$). The
449 difference of performance between Real Tool Use and Mechanical Problem Solving was
450 significantly higher in the SD group than in healthy controls ($U = 400.0, p < .001$) or
451 Alzheimer patients ($U = 329.5, p = .06$), while no difference was found between CBS patients
452 and healthy controls ($U = 140.5, p = .23$). Besides, as can be seen in Figure 2, patients with
453 Alzheimer's disease performed slightly better in Functional/Contextual Associations than in
454 Mechanical Problem Solving ($W = 371.0, p = .016$) whereas patients with semantic dementia
455 exhibited the reverse pattern ($W = 11.0, p = .001$). The difference did not reach significance in
456 the CBS group ($W = 24.0, p = .10$).

457

< Insert Figure 3 about here >

458 3.4. CORRELATIONAL STRUCTURE AND FACTOR ANALYSIS

459 3.4.1. CORRELATION MATRIXES

460 Correlation matrixes are displayed in Table 2 for patients with Alzheimer's disease and
461 semantic dementia. No significant correlation was found in patients with corticobasal
462 syndrome after application of Holm's adjustment for multiple tests (all $ps > .14$). No
463 correlation was found between processing speed assessed by the tracking task and
464 experimental measures, in none of the patients groups (all $ps > .068$).

465 < Insert Table 2 about here >

466 3.4.2. PRINCIPAL COMPONENT ANALYSIS

467 Before going further, it should be acknowledged that due to number of measurements
468 the use of Principal Component Analysis is illustrative at most. Three components were found
469 (eigenvalues = 1.97, 0.67 and 0.34). The first one could be interpreted as the overall
470 performance and explained 66.0 % of data dispersion. It was correlated with all quantitative
471 variables (all $ps < .001$), and it distinguished the AD group from the HC group ($p < .001$). The
472 second dimension accounted for 22.5 % of data dispersion and opposed on the one hand,
473 Mechanical Problem Solving (No-choice) and on the other hand, Functional/Contextual
474 Associations and Single Tool Use. This dimension distinguished the SD group from other
475 groups ($p < .001$). Finally, the third component explained 11.4 % of data dispersion and
476 opposed the Choice and No-choice conditions of Mechanical Problem Solving ($p < .001$).
477 Loadings are available in Supplementary Table 2.

478 Results of the PCA are displayed in Figure 4. On the variables factor map, long vectors
479 are variables for which data dispersion is well explained by the two axes, and the relative
480 directions of vectors indicate associations or dissociations between variables. In this case,
481 Mechanical Problem Solving and Functional/Contextual Associations are clearly dissociated,
482 with Real Tool Use and Single Tool Use being in an intermediate position between these

483 tasks. On the individuals factor map, groups located on the left had poor overall performance,
484 while groups located at the top performed better in Functional/Contextual Associations than in
485 Mechanical Problem Solving. Here, it is clear that SD patients had better performance in the
486 latter than in the former.

487 < Insert Figure 4 about here >

488 3.5. PROFILES

489 As clinical heterogeneity may lead to power problems and distorted inferences in
490 statistical group analyses, a profile analysis was performed. Table 3 provides three key pieces
491 of information: 1) patients with Alzheimer's disease are more frequently impaired in
492 Mechanical Problem Solving than patients with semantic dementia; 2) dissociations between
493 problem solving and picture matching are more frequent in the SD than in the AD group; 3)
494 Real Tool Use and Functional/Contextual Associations are often concurrently impaired in the
495 SD group but not in the CBS group. In addition, Table 4 reveals a double dissociation
496 between semantic dementia and corticobasal syndrome as regards Mechanical Problem
497 Solving and Functional/Contextual Associations (Fisher exact test on 2x4 table, $p = .035$). The
498 same is true between semantic dementia and Alzheimer's disease (Fisher exact test on 2x4
499 table, $p = .001$) so group effects are confirmed at the individual level. Finally, a deficit in both
500 Mechanical Problem Solving and Functional/Contextual Associations is always associated
501 with tool use disorders, regardless of the disease.

502 < Insert Table 3 about here >

503 < Insert Table 4 about here >

504 IV. DISCUSSION

505 The purpose of the present study was to describe tool use disorders in Alzheimer's
506 disease, semantic dementia and corticobasal syndrome with regard to the semantic and
507 technical reasoning hypothesis. We shall now discuss the main results in each patient group
508 and their relationship with neuropsychological data.

509 4.1. RELATIONSHIPS BETWEEN CLINICAL DATA AND TOOL USE DISORDERS

510 Patients were recruited with reference to international consensus criteria and the
511 neuropsychological assessment produced data consistent with diagnosis (Figure 1). All patient
512 groups exhibited tool use disorders so they were all likely to have reduced autonomy when
513 using tools in everyday life. However, demographic data and the MMSE score failed to
514 predict tool use abilities, as previously suggested (Lesourd et al., 2013). Although it is
515 intuitive that as the disease progresses, the growing number of cognitive defects may generate
516 tool use disorders (see for example Ochipa et al., 1992), our data imply that some patients
517 may exhibit tool use disorders even in the very beginning of the disease. In Alzheimer's
518 disease, it might depend on the presence/absence of non-memory cognitive disorders but here,
519 most patients exhibited the amnesic type of the disease (see McKhann et al., 2011). Future
520 studies may compare different phenotypes of Alzheimer's disease.

521 Within-group comparisons and correlations also confirm that Single Tool Use alone
522 cannot predict real tool use abilities (Baumard et al., 2014; Lesourd et al., 2013). In all
523 likelihood, this task is a simulation of real tool use, and hence calls for technical reasoning
524 and semantic memory, but also for additional cognitive mechanisms that were beyond the
525 scope of this study. For example, working memory might be needed to imagine and maintain
526 the object to be used with the tool, as it has been demonstrated for pantomime of tool use
527 (Bartolo, Cubelli, Della Sala, & Drei, 2003). In addition, it must be acknowledged that the
528 clinical rating is frequently more ambiguous for Single Tool Use than for Real Tool Use since
529 only the latter provides clinicians with objective evidence of success or failure. For all these

530 reasons, the most reliable way to detect tool use disorders is probably to ask patients to
531 actually use tools and objects.

532 4.2. TOOL USE DISORDERS IN SEMANTIC DEMENTIA

533 4.2.1. CONFORMITY OF DATA WITH HYPOTHESES

534 The semantic memory hypothesis predicted positive correlations between performance
535 in Functional/Contextual Associations on the one hand, and performance in Single Tool Use
536 and Real Tool Use (Choice condition) on the other hand. In contrast, Real Tool Use (No-
537 choice condition) was expected to be easier. The technical reasoning hypothesis predicted
538 positive correlations between performance in Mechanical Problem Solving tasks and both
539 Single Tool Use and Real Tool Use (both conditions). Regarding these predictions, the fact
540 that patients with semantic dementia had normal performance in Mechanical Problem Solving
541 immediately rules out the technical reasoning hypothesis in this group, while results are
542 consistent with the semantic memory hypothesis. In comparison with healthy controls,
543 patients with semantic dementia have difficulties with Single Tool Use, Real Tool Use and
544 Functional/Contextual Associations but not with Mechanical Problem Solving. In Real Tool
545 Use, the Choice condition was more difficult than the No-choice condition. This deficit in tool
546 selection seems to be specific to familiar tools since it was not observed, or not in the same
547 proportions, in Mechanical Problem Solving (Figure 3). Furthermore, the latter was easier
548 than both Real Tool Use and Functional/Contextual Associations so it is reasonable to assume
549 that the core deficit is at the level of semantic memory rather than technical reasoning or tool
550 application. To sum up, patients with semantic dementia had difficulties in selecting present
551 tools as well as in imagining absent objects.

552 4.2.2. SEMANTIC MEMORY VERSUS TECHNICAL REASONING

553 In the framework of the technical reasoning hypothesis, tool application is a synonym
554 for utilization and depends on this type of reasoning. In our design, Real Tool Use (choice)

555 implied tool selection and tool application while Real Tool Use (no choice) called for tool
556 application only. On this ground, the following results may be highlighted. First, patients with
557 semantic dementia had tool selection deficit. Second, they significantly improved in the No-
558 choice condition compared with the Choice condition. Third, they did not demonstrate tool
559 application deficit in Mechanical Problem Solving. As a conclusion, it can be argued that tool
560 selection is lost whereas tool application is relatively spared. In the field of apraxia,
561 dissociations have already been demonstrated between tool application and knowledge about
562 tool function in stroke patients (see Buxbaum & Saffran, 2002) and Alzheimer patients
563 (Moreaud et al., 1998). It has been proposed that the former relies on technical reasoning
564 while the latter relies on semantic memory, and that both are involved in the use of familiar
565 tools (Goldenberg & Hagmann, 1998; Osiurak, 2014; Osiurak et al., 2011; Randerath,
566 Goldenberg, Spijkers, Li, & Hermsdörfer, 2011). Indeed, previous studies found that some
567 tool use tasks call for semantic memory whereas other call for problem solving skills
568 depending on transparency of mechanical relationships between tools and objects or between
569 different elements of the same device (Hartmann et al., 2005). Notably, technical reasoning
570 may be important to use tool/object pairs (Goldenberg & Hagmann, 1998). Besides, patients
571 with severe semantic loss may remain able to produce tool-related actions that do not
572 correspond to the prototypical use but that are still compatible with the tool's physical
573 properties (Hodges et al., 2000; Osiurak et al., 2008). Consistent with this hypothesis, our data
574 revealed a semantic memory/technical reasoning axis that distinguished patients with
575 semantic dementia from other groups.

576 In all likelihood, patients with semantic dementia had tool selection disorders due to the
577 semantic memory loss but spared tool application thanks to compensations by technical
578 reasoning. The latter may inform individuals about *how to* carry out the action by bringing out
579 possible tasks (e.g., inserting, turning, lifting the key; Osiurak, 2014; Osiurak et al., 2010,

2011). However, taken in isolation these tasks are meaningless in that they do not have any purpose *per se*; they are only technical potentials (e.g., participants could rub or strike the padlock with the key, or even lift the padlock and push the key). On the contrary, semantic memory, which is certainly highly culture-dependent, may inform individuals about *what* to do (or why) but not about how to do it, thus indicating which technical potentials should be considered relevant or irrelevant when using familiar tools and objects, particularly in light of the examiner's expectations (Osiurak, 2014; Osiurak & Badets, 2016). In this view, patients with semantic dementia may be able to identify technical potentials but not the purpose of actions (of which they were not informed). Subsequently, they may select tools depending on tool/object technical complementarity but not in accordance with cultural expectations. As an analogy, these patients are known to process common words as unfamiliar words while reading or writing irregular words and doing so they make errors (e.g., "caught" written as "cort"; Neary et al., 1998), but they remain able to read regular words. Interestingly, the two-way hypothesis (Milner & Goodale, 1995; Ungerleider & Mishkin, 1982) distinguished a dorsal, parietal stream dedicated to the guidance of action and a ventral, temporal stream dedicated to object recognition and representation. Back to our topic, technic-based actions may rely at least on the left parietal lobe (Goldenberg, 2009) whereas culture-based choices may rely on ventral, temporal lobes (see also Hodges et al., 1999).

4.3. TOOL USE DISORDERS IN CORTICOBASAL SYNDROME

4.3.1. CONFORMITY OF DATA WITH HYPOTHESES

As with other groups, patients with corticobasal syndrome exhibited tool use disorders but the underlying reasons are different. This group showed significant impairment in Mechanical Problem Solving but not in Functional/Contextual Associations. Besides, at the individual level, deficits were less frequent in the former than in the latter (i.e., 29 % against 72 %, respectively). Correlations did not reach significance, perhaps because of the low

605 sample size. However, single-case analyses demonstrated that problem solving deficits were
606 always associated with impairment in Real Tool Use. In addition, dissociation was more
607 frequent between Real Tool Use and Functional/Contextual Associations than between the
608 former and Mechanical Problem Solving (Table 4). Interestingly, in Real Tool Use, the
609 impairment did not take the form of tool selection deficits (Figure 3) suggesting tool
610 application was at stake. On the whole, the technical reasoning hypothesis is more plausible
611 than the semantic memory hypothesis, which is logical considering that lesions are more
612 frequent in the frontal and parietal lobes than in the temporal lobes (Litvan et al., 1997).
613 Interestingly, this cognitive pattern demonstrates a double dissociation of problem solving
614 skills and semantic knowledge in corticobasal syndrome and semantic dementia.
615 Notwithstanding, this finding should be interpreted with caution because tool application
616 deficits can be explained in different ways.

617 *4.3.2. TOOL APPLICATION VERSUS TECHNICAL REASONING*

618 Difficulties in tool application can be the consequence of technical reasoning deficits
619 following parietal lobe lesions as it has been described in stroke patients (Goldenberg, 2009;
620 Jarry et al., 2013). Such patients are neither able to select nor to use familiar tools
621 (Goldenberg & Hagmann, 1998). Interestingly, Spatt et al. (2002) described five patients with
622 corticobasal syndrome who had deficits in the selection of novel tools, which may suggest
623 that they did have technical reasoning deficits. However, we did not distinguish scores for tool
624 application and tool selection in Mechanical Problem Solving, and we used combined scores
625 including raw scores and time completion. It turns out that corticobasal degeneration is
626 characterized by bilateral, asymmetric motor deficits due to frontal lobe lesions (Armstrong et
627 al., 2013; Litvan et al., 1997). In addition, according to conception/production models of
628 apraxia (Osiurak, 2014; Rothi et al., 1991, 1997; Roy & Square, 1985), efficient application
629 of tools is not possible in case of conception deficits, and errors in tool application may be

630 accounted for either by isolated motor deficits or technical reasoning deficits, depending on
631 patients. Indeed, it has been demonstrated that the kinematic features of movement depend on
632 the type of gesture to be done (Hermsdörfer, Hentze, & Goldenberg, 2006). Therefore, tool
633 application deficits in this population could be due to either motor deficit or conception (i.e.,
634 technical reasoning) deficit. We shall now discuss these two hypotheses.

635 According to the motor hypothesis, the deficit should be exclusively at the level of tool
636 application while tool selection should be spared. Motor deficits should lead to poor
637 performance in any task involving tool use while other tasks should be spared. Likewise, the
638 “motor” dimension should play a role in both choice and no-choice conditions since both
639 scores took tool application into account. Our data are consistent with this prediction since
640 patients had impaired performance in Single Tool Use, Real Tool Use and Mechanical
641 Problem Solving but not in Functional/Contextual Associations. Besides, the Choice/No-
642 choice difference was not significant in Mechanical Problem Solving. From this point of view,
643 the motor hypothesis is sufficient to explain tool use disorders in corticobasal syndrome.

644 A deficit in technical reasoning should prevent patients from using as well as selecting
645 both novel and familiar tools, as is the case in stroke patients (Goldenberg & Hagmann, 1998;
646 Jarry et al., 2013). Some of our results are in line with this interpretation since CBS patients
647 had impairment in both conditions of Mechanical Problem Solving and Real Tool Use.
648 However, they remained able to select familiar tools, yet this would be very unlikely to occur
649 in case of technical reasoning deficit (see Goldenberg & Hagmann, 1998). On this ground, it
650 can be assumed that their difficulties in tool application were due to motor deficit rather than
651 conception (i.e., technical reasoning) deficit.

652 At this point, our results do not confirm previous findings (Spatt et al., 2002), perhaps
653 because of intrinsic difficulties in diagnosing corticobasal degeneration. We tended to select

654 patients with relatively isolated motor deficits: Five out of seven patients had normal
655 cognitive functioning, and two additional patients were excluded from the sample due to
656 diagnosis uncertainty. In contrast, Spatt et al. found a semantic knowledge breakdown in three
657 out of five patients, which is not typical of the disease. So, lesions were presumably more
658 diffuse in their patients and hence they were more likely to have tool selection deficit due to
659 semantic loss or technical reasoning disorders. To conclude, in order to overcome
660 methodological limitations, future research may analyze problem-solving strategies
661 independently from motor deficits in order to disentangle the motor and technical dimensions.

662 4.4. TOOL USE DISORDERS IN ALZHEIMER'S DISEASE

663 4.4.1. CONFORMITY OF DATA WITH HYPOTHESES

664 Results regarding Alzheimer patients were more delicate to interpret. Based on the
665 technical reasoning hypothesis, a deficit in Mechanical Problem Solving should be associated
666 with a deficit in Single Tool Use and Real Tool Use. This hypothesis appears relevant seeing
667 low performance of Alzheimer patients in Mechanical Problem Solving and correlations
668 between the latter and Real Tool Use. For all that, the semantic memory hypothesis prediction
669 is also relevant seeing positive correlations between Real Tool Use and Functional/Contextual
670 Associations. Besides, these patients exhibited tool selection deficits, although these were not
671 clearly specific to Real Tool Use and less dramatic than in semantic dementia. As a whole, the
672 performance pattern of Alzheimer patients can fit either the semantic memory or the technical
673 reasoning hypotheses (or both).

674 Two conclusions may nonetheless be drawn. First, in the Alzheimer group, deficits are
675 slightly more frequent in Mechanical Problem Solving than in Functional/Contextual
676 Associations (i.e., 66 % against 45 %, respectively). Second, Mechanical Problem Solving
677 deficits are more frequent in Alzheimer's disease than in semantic dementia (i.e., 66 % against
678 31 %, respectively) but they are not specific since such deficits are even more frequent in

679 corticobasal degeneration (i.e., 72 %). In view of these data, even though tool use disorders in
680 Alzheimer's disease have long been considered to result from semantic memory loss (see for
681 example Blondel et al., 2001), the recently proposed concept of technical reasoning (Osiurak
682 et al., 2010, 2011) puts this interpretation into perspective. Actually, using a semantic
683 memory/technical reasoning axis, Alzheimer's disease is closer to corticobasal syndrome than
684 to semantic dementia (Figure 4).

685 Nonetheless, it is not certain that Alzheimer patients consistently exhibit technical
686 reasoning disturbances. Historically, this type of deficit has been studied in stroke patients
687 with lesions in the left hemisphere (Goldenberg, 2009; Jarry et al., 2013). Clinically, these
688 patients cannot manipulate simple tool/object pairs, and they may grasp tools in an ineffective
689 way (e.g., the blade of a knife; see also Randerath, Goldenberg, Spijkers, Li, & Hermsdörfer,
690 2010) and commit "serious" errors (e.g., a fork to eat soup; see Goldenberg & Hagmann,
691 1998; Sirigu, Duhamel, & Poncet, 1991). Yet, the same has not been observed in
692 neurodegenerative diseases, and nor did we. Interestingly, qualitative analyses of mechanical
693 problem solving strategies in stroke patients (Osiurak et al., 2013) and patients with
694 neurodegenerative diseases (Lesourd et al., 2016) revealed that Alzheimer patients use the
695 same strategies as healthy controls while patients with left brain-damage cannot engage in any
696 problem-solving strategy. So, it can be assumed that mechanical problem solving deficits in
697 Alzheimer patients are not the result of tool-specific cognitive impairments but rather of a
698 broad impairment of problem solving skills. Future research may investigate this distinction.

699 4.4.2. THE ISSUE OF HETEROGENEITY

700 In our results, high heterogeneity and double dissociations were observed within the
701 Alzheimer group, which is quite logical as this disease is characterized by a high degree of
702 heterogeneity whether in progression, imaging or clinical manifestations (Komarova &
703 Thalhauser, 2011; Lam, Masellis, Freedman, Stuss, & Black, 2013). Heterogeneity can be

704 understood in three ways. First, tool use disorders in Alzheimer patients may be the
705 consequence of cognitive impairments that were not taken into account in the present work
706 (e.g., general problem solving skills). Second, heterogeneity between patients might be the
707 consequence of heterogeneity *within* patients in that cognitive mechanisms cannot be reliably
708 measured with a single assessment in Alzheimer's disease (Knotek, Bayles, & Kaszniak,
709 1990). Unfortunately, in our design, patients were assessed only once, as is the case in most
710 studies. Third, a lot of patients had various cognitive impairments (i.e., in both Mechanical
711 Problem Solving and Functional/Contextual Associations) and global slowness. This echoes
712 recent studies that consider Alzheimer's disease as a disconnection syndrome between brain
713 regions that remain relatively operational (Delbeuck, Van der Linden, & Collette, 2003).
714 According to this hypothesis, patients with Alzheimer's disease may have a deficit of access
715 to cognitive functions that are altogether spared, and this may prevent the substitution of
716 altered functions by spared ones. This may lead to global hypo-functioning and slowness as
717 well as to high heterogeneity seeing that brain connectivity is likely to be altered in a very
718 singular way between patients.

719 4.5. CONCLUSION

720 The most startling results of the present work can be summarized as follows: (1) We
721 developed an innovative methodology which overcomes the issue of ceiling effects in the
722 field of apraxia (Lesourd et al., 2013); (2) All patients may have tool use disorders and the
723 latter may appear even in the first stages of Alzheimer's disease, but the underlying reasons
724 are different depending on the disease, which implies that future attempts to maintain
725 autonomy should be grounded in detailed evaluation of tool use skills; (3) Tool use disorders
726 can be described with a semantic memory/technical reasoning axis (see also Goldenberg &
727 Spatt, 2009; for a similar dual-route hypothesis, see Hoeren et al., 2013, 2014). Although
728 conceptual apraxia has been proposed to be the consequence of impairment of different types

729 of knowledge (Ochipa et al., 1992), our results can be interpreted in light of a dichotomy
730 between culture-based (ie., semantic memory) and performance-based (i.e., technical
731 reasoning) mechanisms, which is close to the classical distinction between fluid and
732 crystallized intelligence (Cattel, 1963; see also Osiurak et al., in press, for discussion about
733 the link between technical reasoning skills and fluid/crystallized intelligence).

734 In semantic dementia, the loss of tool knowledge leads to difficulties in both imagining
735 absent tools and selecting present tools while tool application is relatively spared thanks to
736 mechanical problem solving skills (see also Hodges et al., 1999, 2000). In other words,
737 patients may use tools in an unusual but effective way (see for example Osiurak et al., 2008)
738 so perhaps caregivers should not expect them to conform to the prototypical use of tools as
739 long as their method is technically relevant (e.g., buttering bread with the handle of a fork).
740 Likewise, in these patients (and only them), pre-selection of tools by caregivers would be
741 highly beneficial. In corticobasal degeneration, the reverse pattern was found, that is, tool
742 application deficits without loss of semantic knowledge. Additional research is needed to
743 disentangle the relative contributions of motor and technical reasoning deficits to tool use
744 disorders. Finally, in Alzheimer's disease, both the technical reasoning and the semantic
745 memory hypotheses appeared relevant depending on patients. Difficulties were frequent in
746 Mechanical Problem Solving but not of the same nature as in stroke patients. All that being
747 said, we found dissociations within each patient group and some patients exhibited tool use
748 disorders without loss of semantic knowledge or problem solving deficits, therefore the
749 technical/semantic axis is not sufficient and additional factors are likely to determine tool use
750 skills in patients with neurodegenerative diseases (e.g., general problem solving skills, the
751 singularity of brain organization and lesion patterns).

752

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988 **LEGENDS FOR FIGURES AND TABLES**989 **Table 1**

990 Data between brackets are standard deviations. Bold values are significant differences
991 between patients and healthy controls.

992 **Table 2**

993 Bold values are significant correlations. RTU = Real Tool Use; MPS = Mechanical
994 Problem Solving; FCA = Functional/Contextual Associations; Irr. T. = Number of irrelevant
995 tools selected in Real Tool Use, Choice condition.

996 **Table 3**

997 Bold values are significant differences.

998 ^a A deficit means that individual's scores are significantly different ($p < .05$) from that of
999 healthy controls.

1000 ^b Classical and strong dissociations have been grouped to summarize the findings.

1001 ^c All analyses were performed using two-by-two tables and Fisher exact test.

1002 STU = Single Tool Use; RTU = Real Tool Use; MPS = Mechanical Problem Solving;
1003 FCA = Functional/Contextual Associations; AD = Alzheimer's disease; SD = Semantic
1004 dementia; CBS = Corticobasal syndrome.

1005 **Table 4**

1006 Values between brackets represent the percentage of these patients who exhibit a deficit
1007 in Real Tool Use (e.g., 32 % of Alzheimer patients had normal performance in Mechanical

1008 Problem Solving and Functional/Contextual Associations but 60 % of these 32 % exhibited
1009 deficits in Real Tool Use).

1010 **Figure 1**

1011 Black lines represent the mean performance of patient groups. Grey dotted lines
1012 represent the cut-off in healthy controls according to French normative data.

1013 **Figure 2**

1014 The boxplots display the interquartile range (minimum, first quartile, median, third
1015 quartile, and maximum). Cases with values more than 1.5 box lengths from the upper or lower
1016 edge of the box are displayed as outliers. The width of boxplots is proportional to the sample
1017 size. Results in the choice and no-choice conditions were averaged for Real Tool Use and
1018 Mechanical Problem Solving. HC = Healthy controls ; AD = Alzheimer's disease ; SD =
1019 Semantic dementia ; CBS = Corticobasal syndrome. Comparisons with healthy controls are
1020 significant with * $p < .05$; ** $p < .01$; *** $p < .001$.

1021 **Figure 3**

1022 Bars represent the percentage of improvement between task 1 and task 2 (e.g., patients
1023 with semantic dementia dramatically improved in the No-choice condition of Real Tool Use).
1024 It is called an improvement because task 1 has always been proposed before task 2. Between-
1025 group comparisons are detailed in the text. Within-group comparisons (Wilcoxon tests)
1026 performed on composite scores were significant with * $p < .05$; ** $p < .01$; *** $p < .001$.

1027 **Figure 4**

1028 Right panel: Solid lines are active variables whereas dotted lines are additional
1029 variables. Details are provided in the text. STU = Single Tool Use; RTU.C = Real Tool Use

1030 (choice); RTU.NC = Real Tool Use (no choice); MPS.C = Mechanical Problem Solving

1031 (choice); MPS.NC = Mechanical Problem Solving (no choice); PS = Processing speed.

1032

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1033

FOOTNOTES

1034

There is no footnote in the manuscript.

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1 **TABLE 1. DEMOGRAPHIC DATA**

	Healthy controls n = 31	Alzheimer's disease n = 31	Semantic dementia n = 16	Corticobasal syndrome n = 7
Gender (women/men)	21/10	21/10	8/8	3/4
Age (years)	75.6 (6.4)	77.1 (7.5)	67.3 (7.4)	71.3 (8.6)
Education (years)	12.4 (4.7)	9.0 (4.4)	12.1 (2.9) ^a	10.3 (3.4)

2

3

4 **TABLE 2. CORRELATION MATRIXES**

	Alzheimer's disease				Semantic dementia			
	RTU	MPS	FCA	Irr. T.	RTU	MPS	FCA	Irr. T.
Single Tool Use	.49	.43	.35	.14	.52	.03	.51	-.65
Real Tool Use		.75	.61	-.28		.31	.95	-.77
Mechanical Problem Solving			.69	-.31			.14	-.23
Functional/Contextual Assoc.				.15				-.68

5

6

7 **TABLE 3. PATIENTS IMPAIRMENTS AND DISSOCIATIONS**
 8 **ACCORDING TO CRAWFORD AND GARTHWAITHE'S (2002,**
 9 **2005) CRITERIA**

	Per cent of patients showing a deficit ^a				Per cent of dissociations ^b		
	STU	RTU	MPS	FCA	RTU-MPS	RTU-FCA	MPS-FCA
AD (%)	17/31 (55)	25/31 (81)	20/31 (65)	14/31 (45)	6/31 (19)	8/31 (26)	1/31 (03)
SD (%)	10/16 (63)	10/16 (63)	5/16 (31)	12/16 (75)	7/16 (44)	1/16 (06)	7/16 (44)
CBD (%)	4/7 (57)	6/7 (86)	5/7 (71)	2/7 (29)	1/7 (14)	4/7 (57)	1/7 (14)
AD vs SD (<i>p</i>) ^c	.758	.289	.037	.067	.095	.138	.001
AD vs CBS (<i>p</i>) ^c	1	1	1	.675	1	.176	.338
SD vs CBS (<i>p</i>) ^c	1	.366	.168	.065	.345	.017	.345

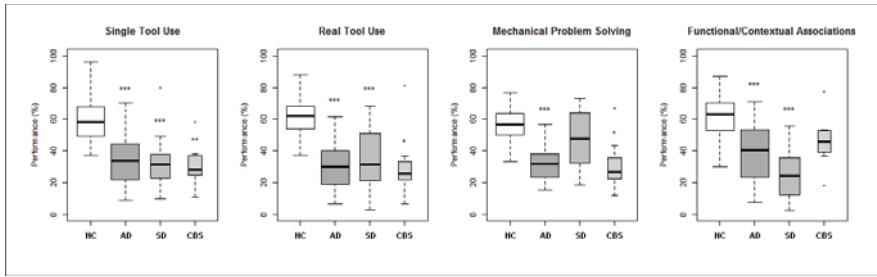
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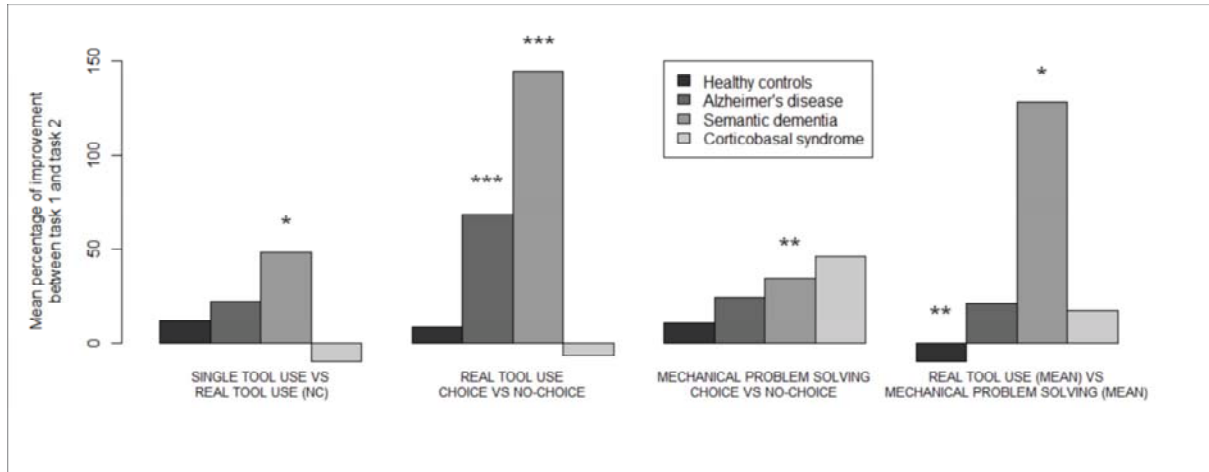
12 **TABLE 4. EFFECTS OF COGNITIVE PROFILES ON TOOL**
 13 **USE ABILITIES**

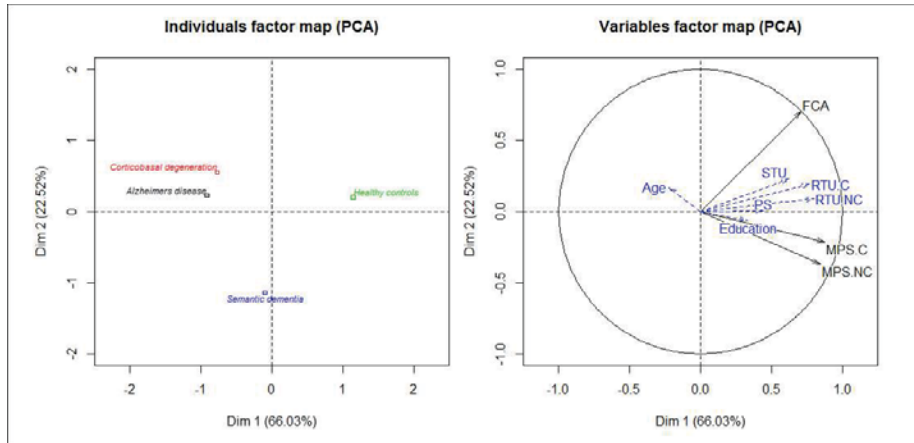
Mechanical Problem Solving	Functional/Contextual Associations	Per cent of patients corresponding to this profile					
		Alzheimer's disease		Semantic dementia		Corticobasal syndrome	
Impaired	Normal	23 %	(71 %)	6 %	(0 %)	43 %	(100 %)
Normal	Impaired	3 %	(100 %)	50 %	(75 %)	0 %	(-)
Impaired	Impaired	42 %	(100 %)	25 %	(100 %)	29 %	(100 %)
Normal	Normal	32 %	(60 %)	19 %	(50 %)	29 %	(50 %)

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