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Research Paper

Cognitive impairments in treatment-resistant depression: Results from the French cohort of outpatients (FACE-DR)

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ABSTRACT

Introduction: Previous studies set out cognitive impairments in major depression. However, only two studies were performed among patients suffering from treatment-resistant depression (TRD) and conducted on limited sample sizes. Here, we aimed to characterize cognitive impairments in TRD, and their association with the severity of depression and daily functioning.

Method: We included 288 patients suffering from TRD (178 women, 52.5 ± 13.1 years old). They undertook sociodemographic, clinical, daily functioning and neuropsychological testing (TMT, Baddeley task, verbal fluencies, WAIS-4 subtests, D2 and RLRI-16). We compared our patients' performances to theoretical performances of the general population.

Results: TRD was associated with poorer neuropsychological performances, except for similarities task. We found an effect of depression severity on processing speed and memory, and an impact on daily functioning affecting memory, selective attention and executive function.

Conclusion: Patients suffering from TRD have significant cognitive impairments. Therapeutic interventions should be developed to manage such impairments.

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1. Introduction

Major depressive disorder (MDD) (American Psychiatric Association, 2013) is a widespread disease considered as a serious public health issue (Sartorius, 2001). Indeed, studies have set out that one patient over three suffering from MDD has to stop working (MorvanYannick, 2007). Also, large cohort studies have reported a high lifetime prevalence of MDD reaching 15–20% in the French population (Haute Autorité de Santé, 2009; Inserm, 2017). This highlights the relevance of developing effective treatment strategies to achieve functional recovery of patients suffering from MDD.

For many years, scientists have developed a great interest in the cognitive functioning in MDD (Polosan et al., 2016). More specifically, researchers have focused on cognitive impairments and meta-analyses tend to confirm such alterations among depressed patients, affecting a wide range of cognitive processes, including verbal memory, processing speed and executive function (Kindermann and Brown, 1997; Rock et al., 2014; Snyder, 2013; Williams et al., 2007). Cognitive deterioration in MDD constitutes an important issue. Indeed, previous results have shown a positive correlation between depressive symptoms and cognitive deficit (Burt et al., 1995). They also have reported that cognitive impairments are associated with a poorer response to antidepressants or more residual symptoms (Gallagher et al., 2013; López-Solà et al., 2020; Pimontel et al., 2016). Finally, all these cognitive alterations seem to be already present at the first episode (Lee et al., 2012) and to persist after clinical remission (Baune et al., 2010; Bhalla et al., 2006; Hasselbalch et al., 2011; Rock et al., 2014). These results are particularly important because cognitive disturbances are associated with social and occupational alterations (Cambridge et al., 2018). In line with this, several studies have found that functional alterations in MDD are greatly or completely mediated by cognitive impairments (Brewster et al., 2017; McIntyre et al., 2013). More specifically, one of them showed that those alterations were fully mediated by executive dysfunction (Knight et al., 2018).

To our knowledge, only two studies have been performed among patients suffering from treatment resistant-depression (TRD), defined as a non-response to at least two antidepressant treatment at appropriate dosage (Fava, 2003). In the first study, 53 subjects with first episode of MDD were compared to the same number of patients suffering from TRD. The results demonstrated poorer performance on executive tasks (TMT-B, Wisconsin Card Shorting Task and Towers of London) in patients with TRD relative to those experiencing a first episode (Rao et al., 2019). These findings confirm the relevance for the assessment of cognitive impairments in TRD. Indeed, patients suffering from TRD tend to have more cognitive deterioration and therefore a more marked impairment in daily functioning (Rao et al., 2019). A second study set out that cognitive deficit is among predictive factors of treatment resistance (López-Solà et al., 2020). This study compared 125 non-treatment-resistant to 104 patients suffering from TRD. It was found that patients with TRD have worse performances than non-treatment-resistant depressed subjects concerning verbal memory, processing speed and executive function.

Therefore, our study aims to identify cognitive impairments in TRD, their association with the intensity of depression and daily functioning. To our knowledge, this is the first study assessing cognitive deficit within a large and a multi-center sample. Such studies are required to facilitate the generalization of the observed effect and to ensure the statistical power to control certain variables such as substance use.

2. Method

2.1. Participants

We recruited 343 depressed patients in the 13 Centers of Expertise for Treatment-Resistant Depression (FACE-DR) that all used the same standardized clinical assessments (Yrondi et al., 2017). Patients were

Table 1
Participants' characteristics.

Field	N	Mean (SD)/ Percent
Demographic information		
Age	288	52.55 (13.5)
Gender		
Male	110	38.19%
Female	178	61.81%
Education level	288	13.01 (3.23)
Illness characteristics		
Illness duration	143	17.38 (11.93)
Number of previous episode	206	5.05 (13.68)
Treatment duration	266	24.7 (48)
Treatment		
Antidepressant		
0 (No)	25	11.7%
1 (Yes)	189	88.3%
Selective Serotonin Reuptake Inhibitors (SSRI)		
0 (No)	143	66.8%
1 (Yes)	71	33.2%
Serotonin-norepinephrine reuptake inhibitor (IRSNA)		
0 (No)	129	62.0%
1 (Yes)	85	38.0%
Monoamine oxidase inhibitors (IMAO)		
0 (No)	159	74.3%
1 (Yes)	55	25.7%
TRICYCLIQUE		
0 (No)	159	74.3%
1 (Yes)	55	25.7%
Second Antipsychotic Generation		
0 (No)	147	68.7%
1 (Yes)	67	31.3%
First Antipsychotic Generation		
0 (No)	187	87.4%
1 (Yes)	27	12.6%
Lithium		
0 (No)	194	90.7%
1 (Yes)	20	9.3%
Antipsychotique		
0 (No)	120	56.1%
1 (Yes)	94	43.9%
ThymoACAE		
0	162	75.7%
1	52	24.3%
Anxiolytics/hypnotics		
0 (No)	100	46.7%
1 (Yes)	114	53.3%
Hypnotics		
0	171	79.9%
1	43	20.1%
Anxiolytics		
0	117	54.7%
1	97	45.3%
Substance consumption		
Cigarette		
No smoker	138	51.1%
Ex-smoker	42	15.6%
Smoker	90	33.3%
Dépendance alcoolique actuelle		
No	234	96.3%
yes	9	3.7%
Abus d'alcool actuel		
No	231	97.5%
yes	6	2.53%
Cannabis		
No	171	94.5%
yes	10	5.5%
Substance		
Cocaine	255	99.0%
0 (unchecked)	2	1.0%
1 (checked)		
THC		
0 (unchecked)	255	99.0%
1 (checked)	2	1.0%
Cannabis		
0 (unchecked)	251	98.0%
1 (checked)	6	2.0%

(*continued on next page*)

Table 1 (*continued*)

Weed		
0 (unchecked)	255	99.0%
1 (checked)	2	1.0%
Shit		
0 (unchecked)	255	99.0%
1 (checked)	2	1.0%
Valium		
0 (unchecked)	253	98.0%
1 (checked)	4	2.0%
Xanax		
0 (unchecked)	254	99.0%
1 (checked)	3	1.0%
Temesta		
0 (unchecked)	254	99.0%
1 (checked)	3	1.0%
Lexomin		
0 (unchecked)	255	99.0%
1 (checked)	2	1.0%
Popers		
0 (unchecked)	255	99.0%
1 (checked)	2	1.0%
Comorbidity		
Current suicide risk		
No	37	15.2%
Yes	207	84.8%
Manic episode		
No	226	99.6%
Yes	1	0.4%
Current manic episode		
No	255	99.2%
Yes	2	0.8%
Past manic episode		
No	255	99.2%
Yes	2	0.8%
Hypomanic episode		
No	227	99.6%
Yes	1	0.4%
Current hypomanic episode		
No	247	96.1%
Yes	10	3.9%
Past hypomanic episode		
No	246	95.7%
Yes	11	4.3%
Hypomanic symptom		
No	223	97.8%
Yes	5	2.2%
Current hypomanic symptom		
No	247	96.1%
Yes	10	3.9%
Past hypomanic symptom		
No	245	95.3%
Yes	12	4.7%
At least two maniac episodes lifetime		
No	121	99.2%
Yes	1	0.8%
At least two hypomanic episodes lifetime		
No	119	99.2%
Yes	1	0.8%
At least two hypomanic symptom lifetime		
No	113	94.2%
Yes	7	5.8%
Current panic disorder		
No	185	80.8%
Yes	44	19.2%
Current panic disorder with current agoraphobia		
No	188	84.7%
Yes	34	15.3%
Current panic disorder without current agoraphobia		
No	203	92.3%
Yes	17	7.7%
Current agoraphobia without a history of panic disorder		
No	189	82.9%
Yes	39	17.1%
Current social phobia		
No	19	33.3%
Yes	38	66.7%

Table 1 (*continued*)

Current post-traumatic stress disorder		
No	230	94.6%
Yes	13	5.4%
Current substance abuse		
No	230	99.1%
Yes	2	0.9%
Mood disorder with lifetime psychotic features		
No	228	95.8%
Yes	10	4.2%
Mood disorder with current psychotic features		
No	228	94.2%
Yes	14	5.8%
Current psychotic syndrome		
No	232	98.13%
Yes	4	1.7%
Lifetime psychotic syndrome		
No	234	99.2%
Yes	2	0.8%
Current generalized anxiety		
No	163	67.6%
Yes	78	32.4%
Past unspecified bipolar disorder		
No	256	99.6%
Yes	1	0.4%

recruited and tested individually during psychiatric consultations. The psychiatrist informed them that the results will be used for research. Suffering from obsessive compulsive disorder, eating disorder or bipolar disorder was defined as exclusion criteria. Undertaking ECT within the past 6 months was also considered as exclusion criteria. Some patients having an history of neurological or sensory disorder, dyslexia, dysorthographia, dyscalculia, dysphasia, dyspraxia, language delay, epilepsy, meningitis, or multiple sclerosis were also excluded ($n = 55$). At the end, 288 patients were enrolled for analyses. As TRD, patients have failed to respond satisfactory to at least two sequential trials with antidepressants of distinct pharmacological classes. After inclusion, they performed a comprehensive, multi-dimensional evaluation comprising an exhaustive biological, medical, psychometric and neuropsychological testing. For this study, we analyzed only the data from both psychometric and neuropsychological assessments. Two hours were required for the neuropsychological evaluation and the order of tests fixed across all the evaluations. Some patients were not able or did not accept to perform every test, explaining the missing data. The characteristics of the overall population are presented in Table 1 and Table 1B..

Table 1B.
Neuropsychological primary outcomes.

	Effectifs	Mean (SD)/ Percent
Coding raw score	196	53.71 (18.40)
Symbols raw score	192	25.19 (9.52)
Digit span raw score	190	23.07 (6.03)
TMT-A time score (sec)	195	45.21 (25.47)
TMT-B time score (sec)	190	106.10 (60.32)
TMT-B-a time score (sec)	184	63.34 (48.69)
Number of words semantic fluencies	193	25.16 (9.22)
Number of words verbal fluencies	193	20.87 (7.75)
Arithmetic raw score	180	13.37 (4.12)
Similarities raw score	188	20.81 (6.40)
D2 raw score	168	336.18 (111.63)
Baddeley Mu score	121	89.87 (15.25)
Immediate recall	192	15.27 (1.38)
Free recall 1	192	8.12 (2.34)
Total recall 1	192	14.52 (1.93)
Free recall 2	192	9.69 (2.57)
Total recall 2	192	15.19 (1.49)
Free recall 3	192	10.72 (2.86)
Total recall 3	192	15.29 (1.67)
Delayed free recall	191	10.97 (3.14)
Delayed total recall	191	15.19 (2.02)

2.2. Measures

2.2.1. Clinical assessment

At baseline, a trained psychiatrist interviewed the participants using the DSM-IV Mini International Neuropsychiatric Interview (MINI) collecting information about the patient's education, marital status, onset and course of MDD, clinical features, and psychiatric comorbidities. Education level was determined as the number of school's years from the first year of primary school. Twelve years correspond to high school diploma.

Current depressive symptoms were assessed using the Montgomery Åsberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979). It is a 10 items semi-structured interview designed to measure depressive symptom severity. Clinician had to rate the different symptoms based on the verbal or non-verbal presentation of the patient. Each item scored between 0 and 6. A greater score indicates more severe depressive symptoms. The French version has demonstrated a good internal consistency (Cronbach's α from 0.85 to 0.94) (Bondolfi et al., 2010). We considered participants under the median (29) as "low-depressed patients" and those above or equal to the median as "high-depressed patients".

Daily functioning was evaluated using the Functional Assessment Short Test (FAST) (Rosa et al., 2007). It is a 24-items semi-structured interview assessing the main areas of functioning (i.e. autonomy, occupational functioning, cognitive functioning, financial problems, interpersonal problems and hobbies). A greater score indicates more important difficulties. The French version has demonstrated good psychometric properties (Cronbach's $\alpha = 0.97$) (Claire et al., 2012). We considered patients showing a score under or equal 21 as having "low levels of impairment in functioning" and those above 21 as having "high levels of impairment in functioning" (Rosa et al., 2007).

2.2.2. Neuropsychological testing

Patients also performed multiple cognitive tasks.

The *RL/RI-16 task* (Buschke, 1984) evaluates verbal episodic memory. Patients had to learn 16 words with a semantic cue associated to each word. Thereafter, they had to recall as many words as they can. After two minutes, cues were given to help patients finding the other words if necessary. Three free and cued recalls were performed immediately after learning with a distractive task between each recall. A recognition task was also made. Patients were asked to recognize the words learned among distractors. A delayed recall was done 20 min after the third recall.

The *D2 task* (Brickenkamp and al, 1999) is a measurement of focused and sustained attention while evaluating selective attention. Patients had to cross d with two lines, among distractors.

The *Trail making test (TMT)* (Reitan, 1955) was used to assess visual scanning and flexibility. In the first condition (TMT-A), patients were invited to connect numbers in ascending order. In the second condition (TMT-B), they were asked to connect alternatively numbers and letters in an assembling or alphabetic order.

Some subtests of the WAIS-IV were also included (Wechsler and Saklofske, 2011).

- Coding assessing processing speed. Patients had to copy as many symbols as possible depending on a discriminative stimulus.
- Symbol search assessing processing speed. Patients had to search symbols among distractors.
- Arithmetic assessing working memory. Patients had to solve orally mathematic problems.
- Digit span assessing working memory. Patients had to memorize and recall digit sequences front order, back order and ascending order.
- Similarities assessing verbal knowledge and abstraction abilities. Patients had to explain the similarities between two concepts.

The *Verbal fluencies test* (Godefroy and Grefex, 2008) evaluated lexical access and flexibility. In a first condition, patients had to provide as many words as possible belonging to a given semantic category (semantic fluencies). In a second condition, participants had to deliver as many words beginning by a letter as possible (phonological fluencies)

In the *Double Baddeley task* (Godefroy and Grefex, 2008), participants had to cross a line and then perform a digit span task. They performed these tasks separately and then underwent both tasks in the meantime. This allows to calculate a Mu score comparing the performance of patients while doing two tasks separately and simultaneously. This measures coordination abilities recruiting the central executive system in the working memory model (Repovs and Baddeley, 2006).

Cut-offs of the different tasks are presented in Tables 2 and 3.

2.3. Statistical analysis

We considered standardized scores for neuropsychological measures. We used normative data of the different tests to transform raw scores in standardized scores. Therefore, we obtained two types of scores: i) ordinal variables: non-continuous percentile; and ii) continuous variables: standard scores, z-scores and continuous percentiles.

For continuous variables, we used Khi2-tests comparison of distribution to a theoretical distribution to assess the performance of the patients as compared to the general population for non-continuous variables. This means TMT scores, fluencies scores and Baddeley tasks scores. We used 95% confidence intervals to identify if more than 5% of the population performed under the 5th percentile. We only use this last method to assess the performance of the RLRI because distribution did not allow a general comparison of the distribution to the general distribution.

For continuous variables, we used t-tests to compare the mean scores of our patients to the theoretical performances. The norms were 10 for the WAIS-IV subtests, 0 for scores measured in standard deviations and 50 for the scores measured in continuous percentile.

Finally, we compared patients above and below the median at the MADRS (=29) to evaluate the associations between depressive symptom intensity and neuropsychological performances. We used Fisher exact test to compare groups for non-continuous variables and t tests for continuous variables. In the same way, we compared patients with low levels of impairment in functioning at the FAST (score under 21) to those with higher scores at the FAST (above 21). Each analysis was performed with and without adjustment for substance use and treatment. Statistical analyses were performed with SAS (release 9.4; SAS Statistical Institute, Cary, NC) and R Statistical Software version 3.4.4. All statistical tests were two-tailed.

3. Results

3.1. Descriptive analyses

We recruited 288 patients (110 women). The mean age was 52.5 years old (SD=13.1). The mean score of the MADRS was 28.8 (SD=6.9). Descriptive data of the ordinal variables are presented in Table 2. Descriptive data of the continuous variables are presented in Table 3.

Table 2
Descriptive data of ordinal variables.

Percentile	*N*	*Percentage (CI, 95%)*
TMT A time percentile		
< 5	15	7.94 (4.5–12.5)
5–10	15	7.94 (4.5–12.5)
10–25	32	16.93 (11.52–22.31)
25–50	57	30.16 (22.81–35.88)
50–75	32	16.93 (11.52–22.31)
75–90	20	10.58 (6.46–15.45)
90–95	8	4.23 (1.90–8.13)
95–100	10	5.29 (2.60–9.41)
TMT time percentile		
< 5	24	12.97 (8.28–18.12)
5–10	13	7.03 (3.78–11.49)
10–25	49	26.49 (19.53–32.24)
25–50	39	21.08 (14.92–26.71)
50–75	30	16.22 (10.89–21.60)
75–90	17	9.19 (5.36–13.95)
90–95	5	2.70 (1.00–6.26)
95–100	8	4.32 (1.94–8.29)
TMT B-A time percentile		
< 5	17	10.37 (6.03–15.59)
5–10	18	10.98 (6.49–16.27)
10–25	43	26.22 (18.86–32.27)
25–50	47	28.66 (20.95–34.73)
50–75	29	17.68 (11.75–23.48)
75–90	2	1.22 (0.2–4.57)
90–95	4	2.44 (0.7–6.22)
95–100	4	2.44 (0.7–6.22)
Semantic fluencies percentiles		
< 5	48	25.40 (18.67–31.08)
5–10	24	12.70 (8.11–17.77)
10–25	43	22.75 (16.40–28.37)
25–50	41	21.69 (15.50–27.28)
50–75	14	7.41 (4.08–11.87)
75–90	10	5.29 (2.60–9.41)
90–95	5	2.65 (0.9–6.14)
95–100	4	2.12 (0.6–5.45)
Phonologic fluencies percentiles		
< 5	21	11.05 (6.83–15.95)
5–10	26	13.68 (8.91–18.82)
10–25	32	16.84 (11.47–22.20)
25–50	42	22.11 (15.87–27.69)
50–75	31	16.32 (11.03–21.64)
75–90	22	11.58 (7.24–16.53)
90–95	5	2.63 (0.93–6.11)
95–100	11	5.79 (2.94–9.98)
Mu Score percentiles		
< 5	18	12.77 (7.51–18.67)
5–10	6	4.26 (1.64–8.94)
10–25	21	14.89 (9.13–20.96)
25–50	33	23.40 (15.93–29.82)
50–75	24	17.02 (10.79–23.22)
75–90	24	17.02 (10.79–23.22)
90–95	3	2.13 (0.5–6.22)
95–100	12	8.51 (4.41–13.95)
Total recall 1		
<5	24	8.33 (5.48–12.21)
Total recall 2		
<5	23	7.98 (5.20–11.81)
Total recall 2		
<5	27	9.37 (6.33–13.40)
Total delayed recall		
<5	31	10.76 (7.48–14.96)
Cut-off: 5%		

Table 3
Descriptive data of continuous variables.

Filed	*N*	*Mean (standard deviation)*	*CI, 95%*	*Cut-offs*
Depression		**MADRS_**		
	288	28.85 (6.93)	28.04–29.67	7
Functional complaint		**FAST_**		
	205	42.10 (13.60)	40.23–43.97	21
Processing speed		**Coding standard score**		
	197	8.03 (3.16)	7.58–8.47	10
		Symbols standard score		
	197	8.58 (2.83)	8.18–8.98	10
Working memory		**Digit span standard score**		
	98	8.89 (2.90)	8.47–9.31	10
		Arithmetic standard score		
	180	8.94 (3.12)	8.48–9.40	10
Selective attention		**D2 GZ-F percentile**		
	168	25.95 (29.19)	21.51–30.39	5
Abstraction		**Similarities standard score**		
	202	11.44 (3.84)	10.95–12.02	10
Verbal episodic memory		**RL/RI free recall 1**		
	192	−0.68 (1.01)	(−0.82)-(−0.53)	−1.65
		RL/RI free recall 2		
	192	−0.74 (1.02)	(−0.88)-(−0.59)	−1.65
		RL/RI free recall 3		
	192	−0.90 (1.19)	(−1.06)-(−0.72)	−1.65
		RL/RI free delayed recall		
	191	−0.93 (1.33)	(−1.12)-(−0.74)	−1.65

D2GZ-F: number of correct targets identified; MADRS: Montgomery & Asberg Depression Scale; FAST: Functional Assessment Short Test

3.2. Comparison to a theoretical distribution

We compared our data distribution to a theoretical distribution for the performances of patients with TRD to that of the general population. We found that patients' distributions are on the left of those in the general population for all cognitive scores, meaning that patients suffering from TRD performed worse than the individuals from the general population for TMT-A time execution (χ^2=*337.9; p < 0.001*), TMT-B time execution (χ^2=*340.9; p < 0.001*), difference of time execution between TMT-B and TMT-A (χ^2=*402.5; p < 0.001*), number of words produced during the semantic fluencies task (χ^2=*457.5; p < 0.002*), number of words produced during the phonologic fluencies task (χ^2=*217.6; p < 0.001*) and the Mu score at the Baddeley task (χ^2=*177.2; p < 0.001*).

In addition to those results, we found that the proportion of patients with TRD under the 5th percentile was greater than that in the general population. This was observed for all results except for the time of execution during TMT-A (see Table 2). The lack of sensitivity of RL/RI ordinal scores did not allow us to perform comparisons of distributions. We only reported the percentage of scores under the 5th percentile. We found significantly more than 5% of our patients under the 5th percentile for total recall 1 (χ^2=*38.2; p < 0.001*), total recall 2 (χ^2=*36.9; p < 0.001*), total recall 3 (χ^2=*44.4; p < 0.001*) and delayed total recall (χ^2=*51.5; p < 0.001*).

3.3. Comparison of mean to a theoretical mean

We used t-tests to evaluate the difference of the performances between our study patients and the general population. We found worse performances within our sample as compared to the general population, except for similarities' performances where patients had greater performance as compared to the general population (*t = 5.49; p < 0.001*). We found worse performance for code standard score (*t=−8.74; p < 0.001*), symbols standard score (*t=−7.03; p < 0.001*), digit memory standard score (*t=−5.26; p < 0.001*), arithmetic standard score (*t=−4.54; p < 0.001*), D2 GZ-F percentile (*t = 10.68; p < 0.001*), RL/RI free recall 1 (*t=−9.3; p < 0.001*), RL/RI free recall 2 (*t=−9.9; p < 0.001*), RL/RI free recall 3 (*t=−10.4; p < 0.001*) and RL/RI delayed free

recall ($t=-971$; $p < 0.001$).

3.4. Correlations between depressive, functioning and neuropsychological variables

Correlations between depressive scores and neuropsychological performances are presented in Table 3. We considered participants showing a MADRS score under the median of 29 as "low-depressed patients" and those with a MADRS score equal or above the median as "high-depressed patients". We found that highly depressed patients performed worse on symbols task ($p = 0.02$), RL/RI free recall 3 ($p = 0.033$), RL/RI free delayed recall ($p = 0.004$) and TMT-A time execution ($p = 0.004$). We performed the same analysis, while controlling the effect of alcohol dependence, cannabis consumption, and hypnotics. In this condition, the effect on the RL/RI free delayed recall still remained significant ($p = 0.022$).

Similarly, we compared patients with low functional impairment having FAST scores under or equal 21 and those with high functional impairment showing FAST scores above 21 (see Table 4). We found that patients with high functional impairment performed worse on RL/RI free recall 1 ($t = 3.27$ $p = 0.007$), RL/RI free recall 2 ($t = 3.55$; $p = 0.003$), RL/RI free delayed recall ($t = 2.29$; $p = 0.022$), arithmetic standard score ($t = 2.08$, $p = 0.037$), D2 GZ-F percentile score ($t = 2.08$; $p = 0.037$) and similarities ($t = 3.16$; $p = 0.007$). We did not find any association for ordinal variables. We performed the same analysis, controlling the effect of on alcohol dependence, cannabis consumption, and hypnotics. In this condition, the effect on the RL/RL free recall 1 ($t = 6.32$; $p = 0.003$), the RL/RI free recall 2 ($t = 2.84$; $p = 0.05$) and the delayed free recall ($t = 3.57$; $p = 0.027$) remained significant.

4. Discussion

The aim of the study was to characterize cognitive impairments in a large sample of patients suffering from TRD. Consistent with cognitive results among depressed patients (Kindermann and Brown, 1997; Rock et al., 2014; Snyder, 2013), we found that patients with TRD performed worse than the general population regarding processing speed and executive function. Indeed, they showed poor performances on code, symbols, arithmetic and digit memory, verbal fluencies, Baddeley, TMT-A, TMT-B and D2 tasks. We also found altered performance in memory through RL/RI scores. However, we reported that patients exhibited better performances on similarities task relative to the general population. This finding was unexpected because similarities are known to assess executive function and verbal knowledge. An explanation is that our sample experiencing a high level of education had better verbal knowledge.

The study also aimed to identify the link between depressive symptoms and neuropsychological performance. We found an effect of depressive symptoms on cognitive functioning mainly referring to processing speed and memory. When controlling for substance use, we only found an effect on memory. This means that more the patients are depressed, more they have deteriorated speed and memory processing. These results are partly congruent with an earlier study showing an effect of depression on almost all cognitive tasks (Burt et al., 1995). This could be explained by the fact that our sample has an important level of depression (medium-severe). Therefore, this could have produced a roof effect on cognitive tasks. Moreover, for executive function, we mainly used categorical variables that may have significantly reduced the statistical power of the analysis. Importantly, the associations between depressive symptom severity and memory performances, when controlling for substance use, is congruent with the impact of such substances on memory function. Indeed, there was a deleterious effect of alcohol (Stavro et al., 2013) and cannabis (Crean et al., 2011) on memory. Also, researchers claimed a negative impact of hypnotics on cognitive performances (Vermeeren and Coenen, 2011). This led to consider that the link between depression and memory is a particularly robust finding in our study.

Finally, we found an association between impaired functioning and cognitive performances. We found that patients showing low levels of functioning worse more than those with normal functioning on memory task, executive task, working memory task and selective attention task. This is congruent with previous studies highlighting the impact of cognitive impairment on daily functioning (Brewster et al., 2017; Cambridge et al., 2018; Knight et al., 2018; McIntyre et al., 2013). However, when controlling for substance use, we only found an association between impaired functioning and memory. This may be explained by the acute effect of substance consumption on cognitive processing (Crean et al., 2011; Tzambazis and Stough, 2000). This would suggest that memory complaints are not only related to cognitive impairments but could also result from acute effects of consumption.

4.1. Implications

Those findings are particularly relevant for psychotherapy, as cognitive deficit has been related to poor outcomes (Bruijniks et al., 2019). Psychological interventions such as Cognitive Behavior Therapy for depression (Beck et al., 1979) may be adjusted to neuropsychological status to optimize patient's learning. In the same way, visual support may help patients to reduce working memory charge and to help long-term learning. Cognitive remediation may also be proposed for TRD patients. First clinical trials have shown a favorable effect of such interventions in this field (e.g., Priyamvada et al., 2015).

4.2. Research perspectives

Until now, research focused especially on cognitive impairments among depressed patients. It would be interesting to study more generally impaired and preserved cognitive abilities in order to identify on which cognitive function we can lean on during psychotherapy. Cognitive functioning in patients suffering from TRD further requires to be compared to that of remitted depressed patients. This would help us to identify if impaired cognitive functioning is predictive of treatment resistance as proposed earlier (Gallagher et al., 2013; Pimontel et al., 2016). In line with this, a particular attention should be paid to examine the impact of neuropsychological impairment on Cognitive Behavior Therapy's efficacy.

4.3. Strengths

This study has some strengths. First of all, the sample size is large. This allows the generalization of the results even if our sample does not perfectly fit the characteristics of the general population because of the high education level. Also, our study sample was characterized by a significant prevalence of males that often lacks in psychological studies. We used a large neuropsychological testing battery that strengthens the validity of our conclusions.

4.4. Limitations

The main limit of our study was to compare patients' performances to theoretical performances. Indeed, a more adapted methodological approach would have been the classical use of a control group.

5. Conclusion

Patients suffering from TRD have cognitive impairments affecting especially processing speed, executive function and verbal episodic memory. The adjustment of psychotherapy and cognitive remediation may be useful to help patients managing with those difficulties in daily life.

Table 4
Association between depressive scores and neuropsychological scores.

	Whole Sample$N = 288$	MADRS (<median)($n = 139$, 49.3%)	(>=median)($N = 143$, 50.7%)	Pvalue	Statistics	OR*	Pvalue*
Age	52.73 (12.8)	52.84 (13.3)	52.44 (12.5)	0.795	0.259		
Sex							
Female	178 (61.8)	87 (62.6)	88 (61.5)	0.855	0.033		
Male	110 (38.2)	52 (37.4)	55 (38.5)				
Mean years of education	13.01 (3.23)	13.21 (3.0)	12.79 (3.5)	0.432	0.785		
Coding standard score	8.03 (3.16)	8.53 (3.2)	7.64 (3.0)	0.050	1.971		
Symbol standard score	**8.58 (2.83)**	**9.09 (3.0)**	**8.16 (2.5)**	**0.020**	**2.338**	1.11	0.205
RL/RI free recall 1	−0.68 (1.01)	−0.54 (1.0)	−0.79 (1.0)	0.092	1.693		
RL/RI free recall 2	**−0.74 (1.02)**	−0.61 (0.9)	−0.84 (1.1)	0.132	1.513		
RL/RI free recall 3	**−0.90 (1.19)**	**−0.71 (1.1)**	**−1.07 (1.2)**	**0.033**	**2.131**	1.43	0.084
RL/RI free delayed recall	**−0.93 (1.33)**	**−0.65 (1.2)**	**−1.23 (1.4)**	**0.004**	**2.837**	**1.56**	**0.022**
Digit span standard score	8.89 (2.90)	9.23 (2.9)	8.62 (2.8)	0.148	1.450		
Arithmetic standard score	8.94 (3.12)	9.26 (3.1)	8.70 (3.2)	0.197	1.289		
D2GZ-F standard score	25.95 (29.29)	29.38 (30.0)	23.06 (28.2)	0.086	1.714		
Similitude standard score	11.34 (3.91)	11.42 (3.9)	11.29 (3.9)	0.815	0.233		

D2GZ-F: number of correct targets identified

* Chi-square test for categorical and Test Student or Wilcox test for continuous variables depending on the distribution.
*Multivariate analysis adjusted on alcohol dependence, cannabis consumption, and hypnotic.

Table 5
Association between daily functioning and neuropsychological scores.

	Whole Sample $N = 288$	FAST (<=21) ($n = 18$, 9.0%)	(>21) ($n = 187$, 91.0%)	Pvalue	Statistic	OR*	Pvalue*
Age	**52.73 (12.8)**	**43.97 (13.1)**	**51.98 (13.3)**	**0.017**	**−2.576**	0.98	0.572
Sex							
Female	178 (61.8)	13 (72.2)	112 (60.0)	0.305	1.048		
Male	110 (38.2)	5 (27.8)	75 (40.0)				
Mean years of education	**13.01 (3.23)**	**14.91 (2.0)**	**13.15 (3.1)**	**0.035**	**2.108**	1.36	0.077
Coding standard score	8.03 (3.16)	9.27 (3.4)	8.05 (3.3)	0.279	1.134		
Symbol standard score	8.58 (2.83)	9.27 (2.9)	8.05 (3.0)	0.467	0.751		
RL/RI free recall 1	**−0.68 (1.01)**	**0.16 (0.9)**	**−0.83 (1.0)**	**0.007**	**3.267**	**6.32**	**0.003**
RL/RI free recall 2	**−0.74 (1.02)**	**−0.01 (0.7)**	**−0.87 (1.0)**	**0.003**	**3.549**	**2.84**	**0.053**
RL/RI free recall 3	−0.90 (1.19)	−0.27 (1.0)	−1.02 (1.2)	0.054	1.926		
RL/RI free delayed recall	**−0.93 (1.33)**	**−0.12 (0.7)**	**−1.09 (1.4)**	**0.022**	**2.289**	**3.57**	**0.027**
Digit span standard score	8.89 (2.90)	10.0 (2.5)	8.99 (3.1)	0.252	1.206		
Arithmetic standard score	**8.94 (3.12)**	**10.8 (2.3)**	**8.88 (3.1)**	**0.037**	**2.08**	1.11	0.497
D2GZ-F standard score	**25.95 (29.19)**	**51.96 (42.4)**	**24.94 (26.9)**	**0.037**	**2.08**	1.01	0.280
Similitude standard score	**11.34 (3.92)**	**13.60 (2.4)**	**11.32 (4.0)**	**0.009**	**3.00**	1.01	0.897

D2GZ-F: number of correct targets identified

*Chi-square test for categorical and Test Student or Wilcox test for continuous variables depending on the distribution.
***Multivariate analysis adjusted on alcohol dependence, cannabis consumption, and hypnotic**.

Ethical approval

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with Helsinki Declaration of 1975, as revised in 2008. The assessment protocol was approved by the institutional review board (French CNIL: DR−2015–673), in accordance with the French laws for non-interventional studies and requires only an informed consent.

Availability of data and materials

The datasets gathered and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

All authors took part in the data collection and data analysis process. The first author wrote the first version of the article. All authors contributed to the critical revision of the article and to the final approval of the version to be published.

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Declaration of Competing Interest

There is no competing interest.

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