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## The relationship between executive dysfunction and neuropsychiatric symptoms in patients with Korsakoff's syndrome

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### ABSTRACT

**Objective:** Patients with Korsakoff's syndrome (KS) show executive dysfunction and neuropsychiatric symptoms. This study investigates whether specific executive subcomponents (shifting, updating, and inhibition) predict variance in neuropsychiatric symptoms. We hypothesized that shifting deficits, in particular, are associated with neuropsychiatric symptoms.

**Method:** Forty-seven patients participated (mean age 61.5; 11 women). Executive function (EF) was measured using six component-specific tasks. Neuropsychiatric symptoms were measured with the Neuropsychiatric Inventory – Questionnaire (NPI-Q). General cognitive functioning was assessed with the Montreal Cognitive Assessment (MoCA). First, factor analysis was conducted to examine shared variance across the EF tasks. Subsequently, a regression analysis was performed with the EF factors and the MoCA as predictors and the NPI-Q as the dependent variable. It was also investigated whether an interaction effect between the EF factors and the MoCA was present.

**Results:** The prevalence of neuropsychiatric symptoms was high (85.7% of the KS patients showed at least one symptom). A two-factor model was extracted with a shifting-specific factor and a combined updating/inhibition factor. The overall regression model was not significant, and no interaction was found between the EF factors and general cognitive functioning. However, a significant relationship between general cognitive functioning and neuropsychiatric symptoms ( $r = -.43$ ;  $p < .01$ ) was detected.

**Conclusions:** Results point at an association between neuropsychiatric symptoms and general cognitive functioning. Possibly, diminished cognitive differentiation in these patients with severe

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cognitive dysfunction accounts for the absence of a significant association between EF and neuropsychiatric symptoms. While the results should be interpreted with caution due to a limited sample size, the found association highlights the need to further unravel the underlying cognitive mechanisms of neuropsychiatric symptoms in patients with KS.

## Introduction

Korsakoff's syndrome (KS) results from thiamine deficiency, mainly occurring in the context of chronic alcohol abuse and limited food intake (Nikolararos et al., 2018; Wijnia et al., 2016), resulting in diencephalic lesions (notably in the mammillary bodies and thalamus; Harding et al., 2000). KS is characterized by chronic and severe cognitive impairments, including anterograde and retrograde amnesia and executive dysfunction. Other notable symptoms include neuropsychiatric symptoms, such as confabulations, apathy, irritability, agitation, aggression, or disinhibition (Arts et al., 2017; Gerridzen et al., 2017). A recent study examining neuropsychiatric symptoms in 281 patients with KS reported that 96.4% of the patients showed at least one neuropsychiatric symptom, with irritability/lability, agitation/aggression, and disinhibition being most prevalent (Gerridzen et al., 2018). Neuropsychiatric symptoms are associated with higher caregiver burden (Chen et al., 2017) and more frequent use of psychotropic drugs (Maust et al., 2017). In addition, patients with KS tend to overestimate their cognitive and functional capacities, typically having limited insight into their own disorder (Egger et al., 2002; Gerridzen et al., 2019), whilst also being institutionalized and dependent on daily care. This may explain the high prevalence of agitation/aggression or disinhibition, as patients assume they do not need the provided care and may show frustration or aggression as a result. This challenging behavior might, in turn, be the reason for the extensively prescribed psychotropic drugs for managing neuropsychiatric symptoms, in addition to the cognitive deficits and comorbid psychiatric illnesses (Gerridzen & Goossensen, 2014).

There is evidence that neuropsychiatric symptoms may be related to executive dysfunction. For instance, in relatively small samples of patients with Alzheimer's disease, associations have been found between executive dysfunction and neuropsychiatric symptoms, especially agitation and disinhibition (Chen et al., 1998), as well as stereotypes and repetitive motor behavior (Gleichgerricht et al., 2011). Apathy has also been repeatedly linked to executive dysfunction (Kawagoe et al., 2017; McPherson et al., 2002). Moreover, a proliferation of research emphasizes the relationship between executive dysfunction, behavioral impairments and psychopathology (Snyder et al., 2015), yet there is no general consensus on whether these are causally related.

There is abundant evidence that patients with KS show executive dysfunction (Brion et al., 2014; Maharasingam et al., 2013; van Oort & Kessels, 2009). Executive functions include higher-order processes such as planning, reasoning and problem-solving, which are important for regulating our thoughts, emotions and behavior (Diamond, 2013). Typically, executive functioning is considered a multifaceted construct that can be subdivided into multiple components. Recent studies argue that

executive subcomponents can be distinguished within a unity/diversity model with a common executive function (common EF; previously described as an inhibition function) on the one hand, and an updating- and shifting-specific factor on the other (Baggetta & Alexander, 2016; Friedman & Miyake, 2017). The common EF variable reflects the ability to maintain and manage goals against all sort of distractors. This ability is measured with a range of inhibition tasks, in which goal maintenance is required. The shifting-specific function reflects the ability to replace goals when necessary, and the updating-specific factor reflects the ability to replace information in working memory whilst preserving some other, relevant information. Recently, patients with KS were found to be predominantly impaired on updating and shifting, while no deficits in inhibition were demonstrated (Moerman – van den Brink et al., 2019).

Studying executive functions in clinical and non-clinical samples is hampered by methodological issues such as the *task impurity problem*. That is, most (traditional) measures of executive functioning are non-specific in nature, tapping into multiple aspects of executive function as well as non-executive abilities, such as memory or motor speed (Kessels, 2019; Packwood et al., 2011; Snyder et al., 2015). A low score on an executive function test can thus be explained by either executive dysfunction itself or by deficits in non-executive abilities. To minimize the influence of non-executive abilities, Friedman (2016) recommended the use of multiple measures of executive functioning with extraction of the common variance in these tasks (by combining them into subdomain scores), thus resulting in a more reliable and valid measure of the ‘pure’ executive function.

To examine the relationship between neuropsychiatric symptoms and executive dysfunction in patients with KS, we propose a theory-driven approach, focusing on the three core executive subcomponents: shifting, updating and inhibition/common EF. These executive subcomponents will be measured with multiple, carefully designed, component-specific tasks of which latent variables will be composed to avoid the aforementioned problem of task-impurity. Previously we showed that KS patients were able to complete these tasks without floor effects (Moerman – van den Brink et al., 2019). We hypothesize a negative correlation between neuropsychiatric symptoms and the performance on executive measures. Previously we found shifting to be mostly affected in patients with KS (Moerman – van den Brink et al., 2019). Deficits in shifting ability may underlie perseverative behavior, problems in dual-tasking, and adaptive behavior in general (Hatoum et al., 2018; Roberts et al., 2007), which are among the main symptoms of patients with KS (Arts et al., 2017; Gerridzen et al., 2017). We also hypothesize that shifting deficits will be the strongest predictor of neuropsychiatric symptoms.

## Materials and methods

### Participants

Forty-seven patients with KS participated in this study, see Table 1 for details. Thirty-seven of these were inpatients of the Korsakoff Centre of Expertise of Atlant, a specialized nursing home for Korsakoff patients in Beekbergen, the Netherlands. Ten of these were inpatients of the Centre of Excellence for Korsakoff and Alcohol-Related Cognitive Disorders of the Vincent van Gogh Institute for Psychiatry in Venray, the

**Table 1.** Descriptive statistics of the sample.

	<i>N</i> = 47	Range
Age, <i>M</i> ( <i>SD</i> )	61.5 (6.6)	38 – 70
Sex, % female	23.4	
Education level, <i>median</i>	4.0	2 – 7
Abstinence in years, <i>M</i> ( <i>SD</i> )	8.3 (6.5)	0.42 – 30.8
NART IQ, <i>M</i> ( <i>SD</i> )	93.0 (19.0)	64 – 127
MoCA, <i>M</i> ( <i>SD</i> )	17.7 (3.9)	10 – 25
NPI-Q	<i>N</i> = 42	
Number of symptoms, <i>M</i> ( <i>SD</i> )	3.7 (2.5)	0 – 9
≥ 1 symptom, %	85.7	
Total severity score, <i>M</i> ( <i>SD</i> )	6.1 (4.8)	0 – 17
Total caregiver distress, <i>M</i> ( <i>SD</i> )	6.0 (6.4)	0 – 23

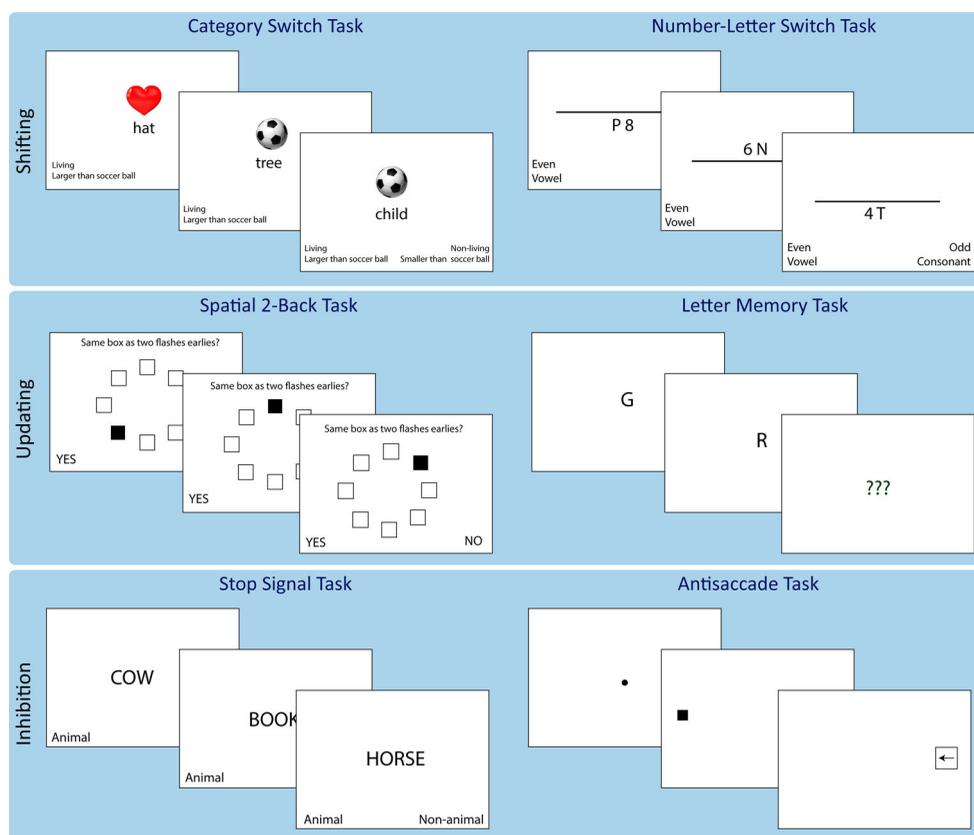
Note. MoCA = Montreal Cognitive Assessment; NART = National Adult Reading Test; IQ = estimate of premorbid verbal intelligence quotient; NPI-Q = Neuropsychiatric Inventory – Questionnaire.

Netherlands. Data of 36 of the 47 patients were already available, as they had participated in our previous study, in which all executive tests and questionnaires were administered (with the executive task results reported in Moerman – van den Brink et al., 2019).

Patients were selected if they met the DSM-5 (American Psychiatric Association, 2013) criteria for alcohol-induced major neurocognitive disorder, amnesic confabulatory type (code: 291.1). Other inclusion criteria were: no additional neurological diagnosis or condition (e.g. stroke) as documented in the medical charts, and aged less than 70 to reduce the possibility that patients are also suffering from a neurodegenerative disease. All patients were in the chronic stage of the syndrome and abstinent from alcohol. Education level was assessed using seven categories based on level of education (in accordance with the Dutch educational system), 1 being the lowest (less than primary school) and 7 the highest (academic degree). The study was approved by the Ethics Committee of the Faculty of Social Sciences of Radboud University (Ref. no. ECSW2015-1210-343) and the institutional review boards of Korsakoff Center Atlant (Ref. no. mdz/mp/2015-005) and the Vincent van Gogh Institute for Psychiatry (CWOP; Ref. no. 15.04365). Written informed consent was obtained for all patients. If the patients were not legally competent, their legal representative also signed the informed consent form.

### Instruments

All participants completed six computerized executive function tasks. These tasks were adapted versions of the tasks Friedman et al. (2008) described and measured the executive components shifting (Category Switch and Number Switch Tasks), updating (Spatial 2-Back and Letter Memory Tasks) and inhibition (Stop Signal and Antisaccade Tasks). The tasks were programmed in PsychoPy version 1.83.03 and reaction times (in ms) were measured with a button-box. All tasks were subdivided into multiple blocks of trials, preceded by practice trials, and only correct trials were used to calculate outcome measures. Task instructions remained visible on the screen during each trial to avoid reduced performance due to memory deficits. The order of the tasks was counterbalanced. All tasks were extensively piloted and modified if necessary, confirming that administering to cognitively impaired individuals was feasible, yet avoiding ceiling



**Figure 1.** Schematic overview of the paradigms tapping into the three executive domains *shifting*, *updating* and *inhibition*.

performance in cognitively unimpaired individuals (see Moerman – van den Brink et al., 2019, for a more detailed description and Figure 1 for a schematic overview of the tasks).

### *Shifting*

The Category Switch Task is designed to measure shifting ability by switching between two tasks: categorizing words into living/nonliving objects versus categorizing the same words into larger/smaller than a soccer ball. 150 ms before each trial, a cue (a picture of a heart for ‘living/nonliving’ and a soccer ball for ‘larger/smaller than a soccer ball’) indicated which instruction should be followed. The dependent variable was the switch cost, calculated as the difference between the median reaction time (RT) of the correct switch trials and the median RT of the correct no-switch trials.

The Number Letter Switch Task also contained switching between two tasks: to indicate whether a number-letter pair (e.g. 4 G, K3) was even/odd or to indicate the same number-letter pair as a vowel/consonant. The position of the number-letter pair (above or below a line) served as a cue for which task to be performed. Switch cost operated as the dependent variable.

### *Updating*

The Spatial 2-Back Task was designed to measure updating ability. In this task, ten squares were placed in a circle. In each trial, one square was briefly highlighted for 500 ms, after which participants had to respond if this square was the same as the one highlighted two trials earlier. Participants were instructed to remember a series of two target locations, while constantly adding a new target location and ignoring the last target location. The dependent variable was the percentage of correct answers.

The Letter Memory Task also required constant updating of information. In this task, a letter was presented on the screen for 2,500 ms after which another letter was presented. After each letter, participants were required to verbally rehearse the last two letters presented. The dependent variable was the percentage of correct answers (as measured by the researcher).

### *Inhibition*

The Antisaccade Task was designed to measure inhibition. In this task, participants were required to attend to the opposite direction of a briefly presented (150 ms) black square (22 × 22 mm), thus inhibiting the automatic tendency to make a saccade to that cue. After this cue, an open square with an arrow (16 mm) was presented at the opposite side for 175 ms, followed by a grey square masking the arrow. Participants were instructed to indicate whether the arrow was pointing to the left or to the right. We measured the percentage of correct answers as the dependent variable.

In the Stop Signal Task, participant first had to categorize a series of words as being an animal or non-animal as fast as possible. After 98 trials, they were instructed not to respond when they heard a tone (100 ms). This signal was presented in 25% of target trials at one of three possible times: 50 ms before the participant's average reaction time (calculated from the practice trials); 225 ms before the average reaction time or 50 ms after the onset of the trial. The dependent variable was the stop-signal RT, calculated following Friedman et al. (2008).

### *Neuropsychiatric symptoms*

Neuropsychiatric symptoms were measured using the validated Dutch version of the Neuropsychiatric Inventory – Questionnaire (NPI-Q; Kaufer et al., 2000; De Jonghe et al., 2003). The NPI-Q is a brief informant version of the standard NPI and measures 12 domains of neuropsychiatric symptom. Caregiver/informants were first asked to indicate whether a symptom is present with “yes” or “no”. In the case of “yes”, informants rated the severity of that symptom on a 3-point Likert scale (“mild”, “moderate” or “severe”). Total severity score is the sum of individual severity scores and can range from 0–36. The NPI-Q is widely used and has acceptable psychometric properties (Kaufer et al., 2000; Tate, 2010). Although informant reports have a potential bias, for instance ratings being affected by the quality of the relationship to the patient, the informant's perspective is likely to be more valid than the ratings from the patients with KS, as they typically lack insight into their own disorder, thus providing a less valid estimate of their neuropsychiatric symptoms (Arts et al., 2017; Gerridzen et al., 2019; Walvoort et al., 2016).

**Table 2.** Descriptive results of the executive function tasks.

	<i>N</i>	<i>M</i>	<i>SD</i>	Min	Max	Skewness <sup>a</sup>	Kurtosis <sup>a</sup>
<b>Shifting</b>							
Category Switch, <i>ms</i>	45	1,265	1,215	−661	5464	1.39	2.83
Number Letter Switch, <i>ms</i>	46	1,611	1,131	−3	4037	0.86	−.20
<b>Updating</b>							
Spatial 2-Back, % correct	45	55.0	16.9	10.4	77.1	−1.34	1.22
Letter Memory, % correct	47	76.3	26.5	11.1	100	−.72	−.29
<b>Inhibition</b>							
Antisaccade, % correct	47	74.5	9.5	50.0	85.2	−.99	.31
Stop Signal, <i>ms</i>	45	540	146	297	963	.44	.19

<sup>a</sup>For accuracy measures, skewness and kurtosis are calculated from arcsine transformed scores.

### Other measures

Intelligence was estimated using the Dutch version of the National Adult Reading Test (NART; Schmand et al., 1992). General cognitive functioning was measured with the validated Dutch version of the Montreal Cognitive Assessment, version 7.1 (MoCA; Nasreddine et al., 2005).

### Procedure

Patients were invited to participate if they fulfilled the inclusion criteria. Assessment sessions lasted up to 1.5 hours and were subdivided into blocks of 30 minutes, if necessary. The MoCA was completed prior to the assessment of the executive tasks. Professional caregivers (patients' primary nurses), who knew the patient well, completed the NPI-Q and provided other data such as demographics, medication use, abstinence period and medical history.

### Data analysis

Results were analyzed using the IBM Statistical Package for the Social Sciences (SPSS) Version 25. Details on the analyses of the executive tasks are described in Moerman – van den Brink et al. (2019). First, a factor analysis was conducted using principal axis factoring and direct oblimin rotation on the six experimental tasks to examine shared variance of the executive function tasks. Subsequently, factor scores were created using regression. Next, a regression analysis was performed to examine whether neuropsychiatric symptoms can be predicted by executive functioning, with the MoCA and the executive factor scores as predictors and the NPI-Q total score as the dependent variable. In addition, two interaction effects were calculated to examine whether the MoCA moderates the relationship between the executive subcomponents and neuropsychiatric symptoms, by multiplying the z-scores of the MoCA and each factor score and adding this score as a predictor in the aforementioned regression analysis. We checked the assumptions of normality for all measures (by examining the P-P plots and the skewness and kurtosis statistics), and checked the specific assumptions for factor analysis and multiple regression analysis (e.g. linearity, homoscedastity, and the absence of multicollinearity).

**Table 3.** Intercorrelations (Pearson's  $r$ ) between the z-scores of the executive function tasks ( $N = 45$ ).

	Category Switch	Number Letter Switch	Letter Memory	Spatial 2-Back	Antisaccade
Number Letter Switch					
$r$	.49**				
$N$	45				
Letter Memory					
$r$	-.08	.26			
$N$	45	47			
Spatial 2-Back					
$r$	-.13	.17	.32*		
$N$	45	47	45		
Antisaccade					
$r$	.03	.28	.27	.50**	
$N$	45	47	47	45	
Stop Signal					
$r$	-.22	-.053	-.23	.27	.01
$N$	45	45	45	45	45

\*  $p < .05$ .\*\*  $p < .001$ .

## Results

Table 1 shows the descriptive statistics of the NPI-Q. Most frequently reported symptoms included agitation/aggression (58.1%), irritability/lability (55.8%) and apathy (48.8%). Descriptive statistics for the executive functioning tasks are presented in Table 2. Table 3 shows three significant correlations, one between both shifting tasks, one between both updating tasks, and one between an updating (Spatial 2-Back task) and an inhibition task (Antisaccade task). The normality assumption was met and no violations of linearity, homoscedastity or multicollinearity were found.

A factor analysis was conducted on the executive function measures. The Kaiser-Meyer-Olkin measure was .55, which is acceptable. Based on eigenvalues  $>1$  and the scree plot, a two-factor model was extracted. Table 4 shows the factor loadings after rotation. Factor 1 represents the shifting ability, while factor 2 is a combined representation of updating and inhibition.

Table 5 shows the relationship between the executive function factors, the MoCA and the NPI-Q. Only the MoCA was significantly related to the NPI-Q. Also, a significant relationship was found between the MoCA and the Updating/inhibition factor. A regression analysis was executed with the NPI-Q as the criterion variable, with the MoCA and two executive factors as predictors. Additionally, to examine whether the MoCA serves as a moderator between the EF predictors and the NPI-Q, two interaction variables (MoCA  $\times$  Shifting; MoCA  $\times$  Updating/Inhibition) were added as predictors to the analysis. The model was not statistically significant ( $F(5,39) = 1.62$ ;  $p = .18$ ), see Table 6.

## Discussion

The aim of the present study was to examine the relationship between executive dysfunction and neuropsychiatric symptoms in patients with KS. With regards to the included executive functions, factor analysis resulted in a two-factor model with a combined factor of updating/inhibition, and a shifting factor. We did not observe any significant relations between these two executive factors on the one hand, and

**Table 4.** Summary of factor analysis for the executive function measures.

	Shifting	Updating/Inhibition
Category Switch task	<b>.798</b>	.108
Number Letter Switch task	<b>.702</b>	-.192
Letter Memory task	-.018	<b>.488</b>
Spatial 2-Back task	.088	<b>.734</b>
Antisaccade task	-.155	<b>.529</b>
Stop Signal task	-.246	-.290

Note. Factor loadings  $>.40$  appear in bold.  $N = 44$ .

**Table 5.** Correlations (Pearson's  $r$ ) between general cognitive functioning, executive functioning and neuropsychiatric symptoms in patients with Korsakoff's syndrome.

	MoCA	Shifting	Updating/inhibition
Shifting			
$r$	.10		
$N$	44		
Updating/inhibition			
$r$	.38*	.03	
$N$	44	44	
NPI-Q			
$r$	-.43**	.03	-.01
$N$	43	40	40

Note. MoCA = Montreal Cognitive Assessment; NPI-Q = Neuropsychiatric Inventory – Questionnaire. \* $p < .05$  \*\* $p < .01$ .

**Table 6.** Linear model of predictors of neuropsychiatric symptoms and their interaction effects.

	$B$	$SE B$	$\beta$	$p$
Constant	6.18	.77		$<.001$
MoCA	-1.88	.79	-.39	.023
Shifting	.31	.92	.06	.740
Updating/inhibition	-.30	.94	-.06	.748
MoCA $\times$ Shifting	.83	.91	.15	.372
MoCA $\times$ Updating/inhibition	-.82	.82	-.16	.325

Note.  $R^2 = .19$ ;  $N = 40$ ; MoCA = Montreal Cognitive Assessment.

informant-based reports of neuropsychiatric symptoms on the other. General cognitive functioning was found to be related to neuropsychiatric symptoms. Finally, we did not find a moderating effect of the MoCA between executive dysfunction and neuropsychiatric symptoms.

In the current patient sample, neuropsychiatric symptoms were very common (85.7% of the patients with KS showed at least one symptom), this prevalence was slightly lower than the 96.4% rate in a sample of KS patients reported by Gerritzen et al. (2018). For comparison, a systematic review of inpatients with dementia shows a mean prevalence rate of 82% of patients having at least one neuropsychiatric symptom (Selbaek et al., 2013). In addition to the brain dysfunction in KS, alcohol use disorder itself co-occurs with other psychiatric conditions (Hasin et al., 2007). These combined factors may explain the high prevalence of the neuropsychiatric symptoms found in KS samples, because some of these symptoms will also occur in the context of a psychiatric disorder.

With respect to executive functions, we found a two-factor model instead of a three- or nested-factor model previously described by Friedman and Miyake (2017). In accordance with earlier findings (Klauer et al., 2010), shifting could be dissociated from

updating and working memory in the current study, with moderate inter-task correlations (.49) between the two shifting tasks and factor loadings  $> .70$ . This is in contrast to updating and inhibition, which could not be differentiated in the current patient sample. A two-factor model of executive function may reflect more unidimensionality within executive function organization in patients with KS than in healthy controls, which is in line with the idea that individuals with lower mental abilities show less differentiated cognitive profiles, also known as Spearman's law of diminishing returns (Spearman, 1927). Low test performances in people with lower mental abilities (due to younger age, lower intelligence or neurological disorders) might thus reflect a (diminished) general ability (*g*) rather than specific cognitive impairment. The unity/diversity model seems to capture the organization of executive functions mainly in cognitively healthy adult populations, which may not be applicable in lower-ability groups (Biesmans et al., 2019; Janssen et al., 2013; Karr et al., 2018). Earlier studies that found a significant association between executive dysfunction and neuropsychiatric symptoms (Brodaty et al., 2012; McPherson et al., 2002) did not take general cognitive functioning into account and used executive measures that could be argued to be task impure. The problem with the latter is that task-impure measures are likely influenced by other abilities such as processing speed, which are related to general cognitive functioning (Floyd et al., 2010; Salthouse, 2005). Studies that did control for general cognitive functioning found significant associations between general cognitive functioning and neuropsychiatric symptoms or apathy, but not for specific executive function measures (Brodaty et al., 2005; Senanarong et al., 2005). Current results suggest similar associations, since general cognitive functioning was correlated to neuropsychiatric symptoms, while the executive measures were not. Notwithstanding the results of the overall regression model, the correlation between general cognitive functioning and neuropsychiatric symptoms ( $r = -.43$ ;  $p < .01$ ; see Table 5), and the magnitude of the standardized beta coefficient of general cognitive functioning ( $\beta = -.39$ ;  $p = .023$ ; see Table 6) confirms the association between general cognitive functioning and neuropsychiatric symptoms.

Some issues concerning task selection should be discussed. Executive dysfunction was measured with experimental tasks for which the psychometric properties (such as reliability and predictive validity) are unknown. However, the tasks used were adapted versions of Friedman et al. (2008), which are widely used to study executive dysfunction and to overcome task-impurity (Friedman, 2016; Snyder et al., 2015). Task adjustments for the current study resulted in a decrease in length and complexity, but did not, in our view, change the nature and validity of the tasks. Additionally, patients as well as cognitively unimpaired controls were able to complete the tasks without floor effects (Moerman – van den Brink et al., 2019). In addition, we did not use the tasks themselves as predictors in our model, but utilized their aggregated measures (established through factor analysis) in order to rule out non-executive task demands such as processing speed, or reading ability as much as possible. Another point of discussion concerns the measurement of neuropsychiatric symptoms. The NPI-Q was designed to measure neuropsychiatric symptoms from a broad spectrum (Tiel et al., 2015). It is possible that executive dysfunction is related to some neuropsychiatric symptoms (Gerridzen et al., 2018), but not to others. Moreover, the distinct

neuropsychiatric symptoms are rated on a 3-point scale and are considered unidimensional, which might not be the case for all neuropsychiatric symptoms. Apathy, for instance, can be considered a multifaceted construct, with the presence of identifiable subtypes (Husain & Roiser, 2018; Radakovic & Abrahams, 2018C; Robert et al., 2010). Previous investigations aimed to identify clusters of neuropsychiatric symptoms on the NPI, such as 'hyperactivity', 'psychosis', 'affective syndrome' and 'apathy' (Aalten et al., 2008). We did not include clusters of the NPI-Q in our analyses due to the modest sample size. Sample size should also be taken into account when interpreting the non-significant results of the model, since general effects may have reached significance if a larger sample size was used. Given the modest sample size, we argue that our results are somewhat equivocal and should be treated with caution. However, while limited from an epidemiological perspective, our sample size of 47 patients with KS is still one of the largest KS samples to date in which detailed cognitive measurements have been performed (with study samples typically consisting of 15 to 25 cases; e.g. El Haj & Nandrino, 2018; Brion et al., 2017; Laniepce et al., 2019). Another point regarding our sample is that some clinical details are not available, such as the age at which KS was diagnosed or the average amount of alcohol consumed previously. However, such information is extremely difficult to validly obtain in patients with KS as most patients are not able to reproduce this information correctly and in many cases there are no relatives who can give this sort of information. It is recommended that future studies, ideally in larger samples, should focus on more in-depth measures of neuropsychiatric and behavioral symptoms.

In sum, neuropsychiatric symptoms are highly prevalent in KS patients, in addition to profound executive deficits (Moerman – van den Brink et al., 2019). A two-factor model of executive function, with shifting and a combined factor of updating/inhibition, was not related to the presence and severity of neuropsychiatric symptoms. General cognitive functioning is found to be related to neuropsychiatric symptoms. Patients with severe cognitive deficits tend to have more neuropsychiatric symptoms. We argue that in patients with KS diminished cognitive differentiation may account for the absence of significant association between executive function and neuropsychiatric symptoms. The high prevalence of both cognitive and behavioral problems in KS motivates the need to investigate both constructs in more detail to develop better treatments or compensatory strategies for patients.

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