Cognitive dysfunction in central disorders of hypersomnolence: A systematic review

Marco Filardi [a], Anita D'Anselmo [a], Sergio Agnoli [b, c], Enrico Rubaltelli [d], Serena Mastria [b, c], Anastasia Mangiaruga [e], Christian Franceschini [f], Fabio Pizza [a, g], Giovanni E. Corazza [b, c, h], Giuseppe Plazzi [g, i, *]

[a] Department of Biomedical and Neuromotor Sciences (DIBINEM), University of Bologna, Bologna, Italy
[b] Marconi Institute for Creativity (MIC), Sasso Marconi, Italy
[c] Department of Electrical, Electronic, and Information Engineering "Guglielmo Marconi", University of Bologna, Bologna, Italy
[d] Department of Developmental and Socialization Psychology, University of Padova, Italy
[e] Department of Medical and Surgical Sciences (DIMEC), University of Bologna, Bologna, Italy
[f] Department of Medicine and Surgery, University of Parma, Parma, Italy
[g] IRCCS Istituto Delle Scienze Neurologiche di Bologna, Bologna, Italy
[h] Université de Paris and Univ Gustave Eiffel, LaPEA, F-92100, Boulogne-Billancourt, France
[i] Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Modena, Italy

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SUMMARY

Central disorders of hypersomnolence (CDH) are characterized by excessive daytime sleepiness not related to comorbid sleep or medical disturbances. We systematically examined scientific literature on cognitive functions in patients suffering from CDH. Forty-eight studies proved eligible and were analyzed separately for Narcolepsy Type 1 (NT1), Narcolepsy Type 2 (NT2), Idiopathic hypersomnia (IH) and Kleine-Levin syndrome (KLS). Results were grouped into the cognitive domains of attention, memory, executive functions and higher order cognition. Consistent attention impairments emerged in NT1, NT2 and IH patients, with NT1 patients showing the most compromised profile. Memory functions are largely unimpaired in CDH patients except for KLS patients who display memory deficit. Executive functions and higher-order cognition have been assessed in NT1 while they received little-to-no attention in the other CDH. NT1 patients display high performance in executive functions but exhibit a complex pattern of impairment in higher-order cognition, showing poor decision-making and impaired emotional processing. Moreover, NT1 patients show increased creative abilities. Assessing and monitoring cognitive impairments experienced by CDH patients will allow the design of personalized interventions, parallel to pharmacological treatment, aimed at improving daytime functioning and quality of life of these patients.

Introduction

Central disorders of hypersomnolence (CDH) are a group of disorders characterized by a primary complaint of excessive daytime sleepiness (EDS) not ascribable to comorbid sleep or medical disorders [1]. CDH include Narcolepsy Type 1 (NT1) and Type 2 (NT2), Idiopathic hypersomnia (IH), Kleine-Levin syndrome (KLS) and insufficient sleep syndrome (ISS). EDS represents the common background feature of these disorders which have different pathophysiology and clinical features. NT1 is characterized by dissociated REM sleep manifestations (cataplexy, sleep paralysis, hypnagogic/hypnopompic hallucinations) and disrupted nocturnal sleep. NT1 pathophysiology is linked to the loss of hypocretinergic neurons in the lateral hypothalamus and low cerebrospinal fluid hypocretin-1 levels [2]. NT1 and NT2 share all symptoms but cataplexy, which is absent in NT2. The neurobiological process involved in NT2 is more elusive as the hypocretinergic system is generally intact or only partially compromised [3]. IH is characterized by EDS associated with long-lasting and non-refreshing naps. Nocturnal sleep can be abnormally long and is often accompanied by remarkable sleep inertia [4]. KLS is a rare disorder of unknown etiology characterized by recurrent episodes of hypersomnolence associated with cognitive and behavioural disturbances [5]. The review's aim is to update the current knowledge of the prevalence of cognitive deficits among

* Corresponding author. IRCCS, Istituto delle Scienze Neurologiche di Bologna, Via Altura n°3, 40139 Bologna, Italy. Fax: +39 051 4966176.
E-mail address: giuseppe.plazzi@unibo.it (G. Plazzi).

Abbreviations

CDH	central disorders of hypersomnolence
EDS	excessive daytime sleepiness
NT1	Narcolepsy type 1
NT2	Narcolepsy type 2
IH	Idiopathic hypersomnia
KLS	Kleine-Levin syndrome
ISS	Insufficient sleep syndrome
OSAS	Obstructive sleep apnea syndrome
RTs	reaction times
ERP	event related potential
CPT	Continuous performance test
SART	Sustained attention to response task
PVT	Psychomotor vigilance task
PET	positron emission tomography
WMS	Wechsler memory scale
CBTT	Corsi block-tapping test
fMRI	functional magnetic resonance imaging
CVLT	California verbal learning test
TMT	Trail making test
WCST	Wisconsin card sorting test
IGT	Iowa gambling task
GDT	Game of dice task
IST	Information sampling task
COWAT	Controlled oral word association test

CDHs by comparing results of studies that investigated patients through neuropsychological tests and studies that investigated the neurocognitive mechanisms linked to psychometric performances of NT1, NT2, IH and KLS patients.

Method

We conducted a systematic search of databases to identify analytical cross-sectional studies published in peer-reviewed journals over the past 20 years (January 2000–2020). Literature search was conducted in accordance with the PRISMA® statement [6] (see Supplementary materials). Forty-eight studies proved to be eligible for inclusion (See Fig. 1) among which the great majority (39) specifically focused on NT1 patients. Thirty-five studies (73%) assessed a sample of untreated (either drug-naive or drug-free) CDH patients, 10 (21%) assessed a mixed sample of treated and untreated patients and three studies (6%) assessed patients under stable pharmacological treatment. Since Raam's study reported on a mixed population (NT2/IH), we decided to include this study in the IH section being the sample mostly composed by IH patients (10/13 were IH) [7].

Detailed information for each study is reported in Table 1. Cognitive functions were studied with a wide array of neuropsychological tests (see Table 2) and procedures that have been grouped according to a reference taxonomy (see Box 1) [8,9].

Narcolepsy Type 1

Forty-three studies assessed cognitive functions in NT1; 32 compared NT1 patients to healthy controls and 11 compared NT1 patients to healthy controls and patients suffering from CDHs or other sleep disorders (primary insomnia and obstructive sleep apnea syndrome, OSAS).

Attention

Alertness

Phasic alertness (rapid mobilization of resources to process an expected stimulus), tonic alertness (ability to maintain attention over a long period of time) and alertness reaction (difference in reaction times between tonic and phasic alertness) have been investigated by means of simple and forewarned reaction times (RTs).

Naumann found no differences in phasic and tonic alertness between NT1 patients and controls [10]. Kotterba reported reduced alertness reaction in NT1 patients compared to controls although with high inter-individual differences [11]. Rieger reported slower and more variable RTs and a remarkable decline in RTs as time-on-task increases, but did not find impaired alertness reaction [12]. Bayard assessed phasic and tonic alertness in NT1, NT2 and controls. NT1 patients displayed slower and more variable RTs compared to controls and NT2 patients [13]. Ramm assessed tonic and phasic alertness in NT1, IH, controls and subjects who complained chronic EDS but did not fulfill the neurophysiological criteria for a CDH diagnosis (subjective EDS) [7]. NT1 patients displayed slower RTs in tonic but not in phasic alertness compared to controls. Ha administered the reaction unit test (reaction speed to different stimulation modalities: visual, auditory and audio-visual) [14]. NT1 responded more slowly than controls to acoustic and visuoacoustic stimuli, while no difference was observed for the simpler visual stimuli. Attentive information processing and attentional allocation have been investigated through event-related potentials (ERP), scalp recorded fluctuations time-locked to the onset of a specific stimulus event.

Naumann assessed attentive and preattentive mechanisms through the auditory P300 (P3) and the mismatch negativity (MMN) components [15]. NT1 patients displayed increased P3 amplitude for the infrequent incoming stimuli, especially over frontal recording sites, which indicate reduced habituation to task-relevant deviant stimuli. Both NT1 and controls showed a clear MMN in the deviant-standard difference waves; however, while controls showed the laterality pattern of MMN amplitude (larger over the right than the left hemisphere) in NT1 patients this asymmetry was absent. Saletu assessed amplitude, latency and the regions involved in the source of N1, N2, P2 and P3 components (auditory oddball paradigm) [16]. NT1 patients displayed prolonged latencies and reduced amplitudes in N2 (central, temporal and frontal sites) and P3 (whole brain) components compared to controls, while no difference emerged in the N1 and P2 components. Low-resolution electromagnetic tomography revealed reduced N2 (medial precuneus) and P3 sources (bilateral precuneus, anterior/posterior cingulate gyri, ventrolateral prefrontal cortex). Total sample assessed: 131 NT1 compared to 22 NT2, 14 IH, 13 subjective EDS and 148 healthy controls.

Selective attention

Selective attention describes the ability to prioritize the information processing of specific stimuli while suppressing responses to irrelevant stimuli. Selective attention has been assessed with tasks requiring participants to mark, as fast and accurately as possible, all target stimuli within the allotted time. Relevant measures are the time needed to complete the task, the number of correctly identified targets, and the error rate. Rieger showed no differences in error rate and search strategy between NT1 patients and controls [12]. Three studies used the d2 attention test. Naumann and Zamarian showed that NT1 patients processed fewer items compared to controls; Zamarian also reported increased errors in patients compared to controls [10,17]. In the study of Delazer NT1 patients displayed a

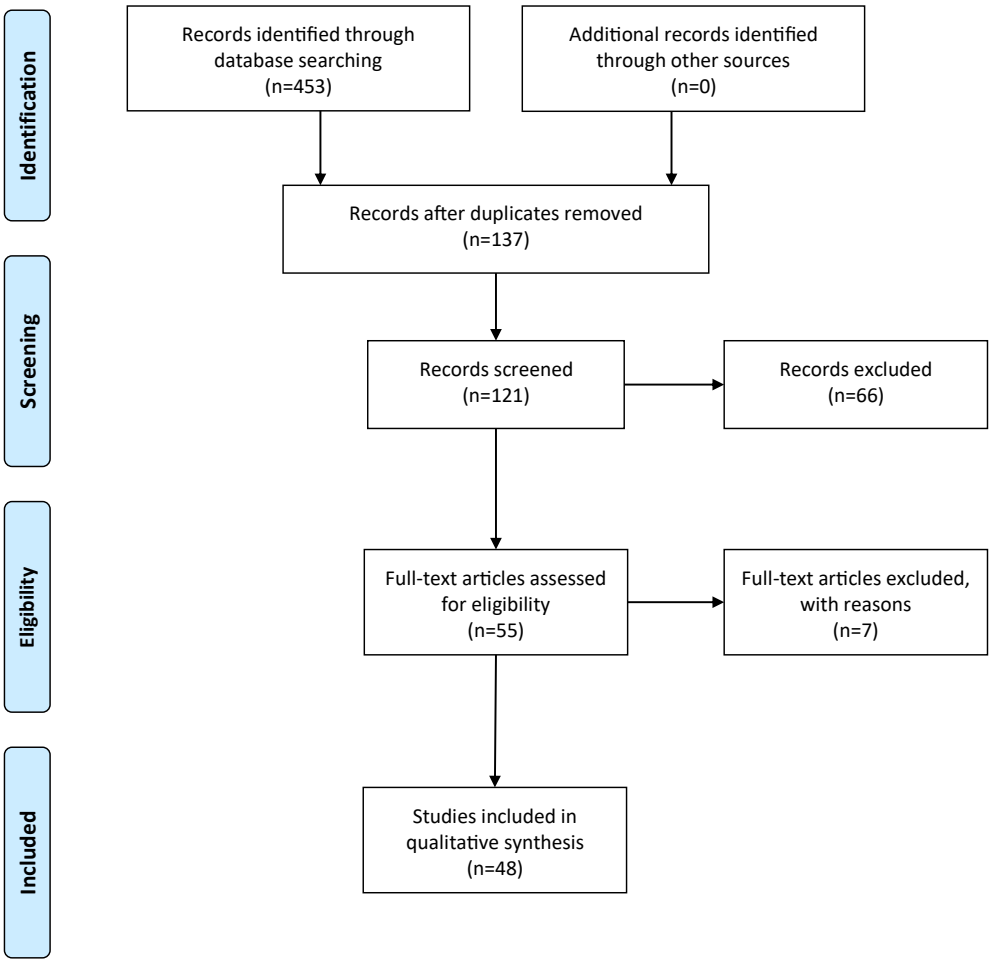

Fig. 1. Flow diagram for studies selection process (from January 2000 to January 2020).

performance within the normal range of controls [18]. In two separate studies Raam assessed selective attention in NT1 patients compared to IH, subjective EDS and controls.

In the first study, the authors found more lapses in NT1 patients than in controls, but no difference emerged with IH patients and subjective EDS [7]. In the second study, the authors reported increased errors in NT1 patients compared to controls [19]. Saletu administered the psychomotor activity test without showing differences between NT1 and controls [16]. Schneider assessed the time course of selective attention in NT1, OSAS, insomniacs and controls [20]. NT1 patients displayed overall the worst performance and presented a peculiar time course of selective attention (performance decrease from 8:00 to14:00 and increase from 14:00 to 18:00) while other sleep disorder patients and controls did not show major fluctuations of performance. Total sample assessed: 152 NT1 compared to 28 IH, 13 subjective EDS, 20 OSAS, 10 primary insomnia and 195 healthy controls.

Divided attention

Divided attention refers to the ability of processing multiple sources of information concurrently. It has been investigated with behavioural paradigms entailing different subtasks (usually visual and acoustic) performed both independently and simultaneously (dual-task condition). Relevant measures are error rate, errors on dual-task condition and RTs. Kotterba reported normal divided attention in NT1 [11]. Naumann did not find increased error rate, but reported slower RTs in NT1 compared to controls [10]. Rieger reported slower and more variable RTs and increased error rate in NT1 patients than controls; moreover, NT1 display a tendency to make more errors in the dual-task condition [12]. Finally, Raam compared NT1 to IH, subjective EDS and controls. NT1 patients displayed slower RTs than controls and more errors compared to IH patients and controls [7]. Total sample assessed: 56 NT1 compared to 14 IH, 13 subjective EDS and 65 healthy controls.

Sustained attention and vigilance

Sustained attention and vigilance, i.e., the ability to focus on a stimulus over a long period of time, has been assessed through tasks that require responding to rarely and irregularly occurring stimuli. In sustained attention tasks, the rate of target stimuli is typically higher than in vigilance tasks. Performance is reflected by omission and commission errors and overall error rate. Kotterba reported no difference between NT1 and controls [11]. Ha showed that NT1 patients made more omission and commission errors on the vigilance task and more omission errors on the continuous performance test (CPT) than controls [14]. Ramm showed that NT1 display slower RTs and made more omission errors than controls and IH patients [7]. In a subsequent study Raam reported an increased error rate in NT1 than in IH patients. Moreover, NT1 displayed an increase in omission errors from the first to the second half of the task [19]. The sustained attention to response task (SART) has been used in three studies. Fronczek reported increased error rate and broader error rate variability in NT1 patient than controls [21]. Van Schie administered the SART to NT1, NT2, IH and OSAS and did not find

Table 1
Summary of studies included within the review.

Reference	Sample	Mean age	Age at onset	Treatment	Cognitive Measures	Other Measures	Procedure
Bayard et al. [43] 2011 France	23 Narcolepsy with Cataplexy (ICSD-2) 23 healthy controls	38.4 ± 14.9 38.5 ± 14.6	19.13 ± 15.34	10 drug naïve 13 drug free (one month)	**Decision Making** Iowa gambling task **Decision Making under risk** Game of Dice	**Sleepiness** ESS MSLT ***Depression*** BDI-II Impulsive Behavior UPPS	Participants were tested individually in a 40-min session. Neuropsychological evaluation was performed from 9:00 to 12:00 between the MSLT sessions.
Bayard et al. [13] 2012 France	22 Narcolepsy with Cataplexy (ICSD-2) 22 Narcolepsy without Cataplexy (ICSD-2) 32 healthy controls	36.2 ± 15.2 29.14 ± 12.5 30.22 ± 8.3	22.3 ± 10.3 20.3 ± 9.6	7 drug naïve 15 drug free (one month) drug naïve	**Alertness** Simple/Forewarned RT **Working Memory** 2-back **Inhibition** Go/No-Go **Flexibility** Flexibility task	***Sleepiness*** ESS MSLT **Depression** BDI-II ***Self-Evaluation Attention*** Self-evaluation attention questionnaire (QAA)	Participants were tested after the first MSLT sessions (9:00)
Bayard et al. [44] 2013 France	41 Narcolepsy with Cataplexy (ICSD-2) 37 Narcolepsy with Cataplexy under psychostimulant 32 healthy controls	34.8 ± 13.1 35.7 ± 15.1 35.6 ± 12.2	20 ± 9.5 15.5 ± 12.3	drug naïve All patients on stable therapy	**Decision Making** Iowa gambling task **Decision Making under risk** Game of dice	**Sleepiness** ESS MSLT MWT ***Depression*** BDI-II Impulsive Behavior UPPS ***Reading Test*** National adult reading test	Drug-naïve patients were tested after the first MSLT sessions (9:00) in a 40-min session Patients taking psychostimulants were tested from 9:00 to 12:00 between the MWT sessions.
Cipolli et al. [37] 2008 Italy	17 Narcolepsy with Cataplexy (ICSD-2) 12 healthy controls	29.94 ± 4.80 30.47 ± 5.16	N/A	drug naïve 2	**Declarative Memory** Memory Quotient (WMS) **Reasoning** Baddeley's Logical Reasoning **Set-Shifting** Trail Making Test (A-B) **Intelligence** WAIS-R	**Sleepiness** ESS ***Depression*** BDI	N/A
Cipolli et al. [38] 2009 Italy	22 Narcolepsy with Cataplexy (ICSD-2) 22 healthy controls	30.23 ± 6.63 29.73 ± 6.07	N/A	drug naïve	**Declarative Memory** Memory Quotient (WMS) **Procedural Memory** Texture discrimination Task **Reasoning** Baddeley's Logical Reasoning **Set-Shifting** Trail Making Test (A-B) **Intelligence** WAIS-R	**Sleepiness** ESS ***Depression*** BDI	Three experimental sessions: training, 1st-d retrieval and 7th-d retrieval
De Zambotti et al. [47] 2014 Italy	12 Narcolepsy with Cataplexy (ICSD-2) 12 healthy controls	33.3 ± 9.4 30.9 ± 9.5	32.3 ± 9.3	drug naïve	**Emotional Process** Humour judgement paradigm	**Sleepiness** SSS ***Depression*** BDI ***Anxiety*** STAI ***Coping Strategies***	Experimental session lasted about 30 min and was performed in the late morning (10:30–13:30) A brief nap was allowed prior to the test

						Coping orientation to problems experienced	
Delazer et al. [18] 2011 Austria	21 Narcolepsy with Cataplexy (ICSD-2) 58 healthy controls	39.71 ± 10.69 41.02 ± 13.30	23.14 ± 9.06	9/21 on stimulants	**Selective Attention** d2 Test **Memory span** Digit span forwards/ backwards **Inhibition** Go-NoGo **Set-Shifting** Intra/Extra dimensional set shift **Planning** One touch stockings of Cambridge **Decision Making** Information sampling task Iowa gambling task **Fluency** Verbal fluency test (Animals/S-words/Fruits-sports) **Intelligence** Vocabulary task	**Sleepiness** ESS SSS MSLT ***Anxiety-Depression*** HADS	The SSS was administered prior to and after the neuropsychological evaluation. Information on times and procedures of neuropsychological assessment are not reported
Dimitrova et al. [24] 2011 Netherlands USA	30 Narcolepsy with Cataplexy (ICSD-2) 15 Narcolepsy without Cataplexy (ICSD-2) 32 healthy controls	36.4 ± 13.6 39.37 ± 13.1 35.5 ± 13.5	N/A N/A	All patients on stable therapy All patients on stable therapy	**Sustained Attention and Vigilance** Psychomotor Vigilance task (PVT) **Decision Making** Balloon analogue risk task (BART)	***Sleepiness*** ESS MSLT ***Anxiety-Depression*** BDI-II HADS Beck Anxiety Inventory ***Impulsive Behavior*** Eysenk Impulsiveness Scale ***Sensation Seeking*** Zuckerman Sensation Seeking Scale ***Eating disorder*** Binge Eating Scale ***Alcohol e Substance abuse*** Alcohol Use disorders Test CAGE questionnaire ***Gambling*** Gamblers Anonymous 20 Questions	The BART was administered twice (30 trial for each session) After a 5-min break subjects performed the PVT (10 min)
Engström et al. [55] 2009 Sweden	8 Kleine-Levin Syndrome (ICSD-2) 12 healthy controls	27 ± 4.2 24	N/A	7/8 drug free	**Working memory** Working memory Task (delayed recall of sequence from the reading span task)	***Neuroimaging*** fMRI	All patients were tested during the asymptomatic period
Engström et al. [56] 2013 Sweden	18 Kleine-Levin Syndrome (ICSD-2) 26 healthy controls	25.9 ± 11.4 24.1 ± 5.3	15.5 ± 1.3	7/8 drug free	**Working memory** Working memory Task (delayed recall of sequence from the reading span task)	***Neuroimaging*** fMRI	All patients were tested during the asymptomatic period
Engström et al. [57] 2014 Sweden	18 Kleine-Levin Syndrome (ICSD-2) 26 healthy controls	25.9 ± 11.4 24.1 ± 5.3	14.4 ± 2.1	7/8 drug free	**Working memory** Working memory Task (delayed recall of sequence from the reading span task)	***Neuroimaging*** fMRI	All patients were tested during the asymptomatic period
Filardi et al. [28] 2017 Italy	21 Narcolepsy Type 1 (ICSD-3) 15 Narcolepsy Type 2	36.19 ± 11.94 35.53 ± 12.95 34.95 ± 11.52	N/A	drug naïve drug free	**Complex Attention** **Measure** Attention network test	***Sleepiness*** ESS MSLT ***Anxiety-Depression***	Participants were tested individually at 10:00 (12 min) Participants were invited to

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Table 1 (*continued*)

Reference	Sample	Mean age	Age at onset	Treatment	Cognitive Measures	Other Measures	Procedure
	(ICSD-3) 22 healthy controls					BDI STAI ***Hyperactive Behavior*** Adult ADHD Self–Report Scale ***Obsessive-Compulsive Behavior*** reduced obsessive-compulsive inventory	take a brief (maximum 30 min) nap if they felt sleepy.
Fronczek et al. [21] 2006 Netherlands	15 Narcolepsy with Cataplexy (ICSD-2) 15 healthy controls	30-36 (range) 28-39 (range)	N/A	13 drug naïve 2 drug free (at testing)	**Sustained Attention and Vigilance** Sustained attention to response test (SART)	***Sleepiness*** ESS MSLT	The SART was administered five times, between each MSLT sessions.
Ha et al. [14] 2007 South Korea	24 Narcolepsy with Cataplexy (ICSD-2) 24 healthy controls (IQ-matched)	30.79 ± 12.84 30.25 ± 8.99	N/A	drug naïve	**Alertness** Reaction unit test **Sustained Attention and Vigilance** Continuous performance test Vigilance test **Working Memory** Corsi block tapping test Work performance series **Flexibility** Cognitrone Determination unit **Reasoning** Raven's progressive matrices Hypothesis formation test	N/A	Participants were tested individually at 10:00 (max duration 180 min) **Test order:** Vigilance test –Continuous performance test –Corsi block tapping test –Ravens progressive matrices –cognitrone –lunch break– Work performance series –hypothesis formation test –determination unit–reaction unit.
Huang et al. [26] 2018 China	104 Narcolepsy Type 1 (ICSD-3) 29 Narcolepsy Type 2 (ICSD-3) 26 healthy controls	20.09 ± 9.13 19.25 ± 5.6 19.10 ± 5.31	12.8 ± 5.2 11.71 ± 3.04	drug free for minimum 7 days drug free for minimum 7 days	**Sustained Attention and Vigilance** Continuous performance test (CPT) **Set-Shifting** Wisconsin Card Sorting Test	***Sleepiness*** ESS PDSS MSLT ***Neuroimaging*** Positron Emission Tomography (PET)	Neuropsychological tests were performed at 8:45 (30-min) immediately prior to the PET study
Joo et al. [41] 2012 South Korea	36 Narcolepsy with Cataplexy (ICSD-2) 36 healthy controls	29 29	16.4 ± 6.4	drug naïve	**Visual memory** Rey complex Figure Test **Learning** Korean California Verbal Test	***Sleepiness*** MSLT ***Depression*** BDI ***Neuroimaging*** Structural magnetic resonance imaging	N/A
Khatami et al. [46] 2007 Switzerland	14 Narcolepsy with Cataplexy (ICSD-2) 10 healthy controls	32 ± 9 29 ± 8	N/A	drug free	**Emotional Process** Humour judgement paradigm	***Sleepiness*** ESS Ullanlinna Swiss–Narcolepsy Scale Stanford Cataplexy Scale ***Anxiety-Depression*** BDI STAI ***Neurophysiological*** Assessment of the startle reflex	Participants were presented 54 pictures (equal numbers of unpleasant, neutral and pleasant pictures) Startle probes (white-noise burst, 50 ms, instantaneous rise time) were applied 3–5 s after picture onset.
Kim et al. [31] 2016 South Korea	33 Narcolepsy with Cataplexy (ICSD-2) 31 healthy controls	27 ± 5 .88 27.16 ± 5.27	14.79 ± 2.79	drug free	**Complex Attention Measure** Digit symbol test **Memory Span** Digit Span forwards/	***Sleepiness*** ESS ***Sleep Quality*** PSQI ***Depression***	Participants were tested individually in a 2.50 h session. Information on times and procedures of MRI scan are not reported

					backwards **Visual memory** Rey complex Figure **Working Memory** Corsi block tapping test **Inhibition** Stroop test **Set-Shifting** Trail Making test A-B **Fluency** Controlled Oral Word Association Test **Learning** Korean California Verbal Test	BDI-II ***Neuroimaging*** Structural magnetic resonance imaging	
Kotterba et al. [11] 2004 Germany	13 Narcolepsy with Cataplexy (ICSD-2) 10 healthy controls	41.5 ± 12. 9 55.1 ± 7.8	N/A	8/13 drug free	**Alertness** Simple RT **Divided Attention** Divided and Continuous Attention Test **Sustained Attention and Vigilance** Vigilance Test **Driving simulator** Computer Aided Risk simulator	***Sleepiness*** ESS	N/A
Lacaux et al. [52] 2019 France Italy	131 Narcolepsy Type 1 (ICSD-3) 54 Narcolepsy Type 2 (ICSD-3) 126 healthy controls	35.32 ± 16.27 38.35 ± 15.07 33.6 ± 15.2	12.8 ± 5.2 11.71 ± 3.04	23/131 drug free 7/54 drug free	**Creativity** Evaluation of potential creativity test battery	***Sleepiness*** ESS MSLT ***Anxiety-Depression*** HADS ***Creative identity*** Test of Creative Profile Creative Achievement Questionnaire	Formal test of creativity was conducted in a subset of 30 patients and controls Participants were tested individually in a 2.50 h session. A 30-min planned break was included and 6/30 participants slept during the break
Landtblom et al. [53] 2003 Sweden	4 Kleine-Levin Syndrome (ICSD-2)	19-30 (range)	13-18 (AO)	All on pharmacological polytherapy	**Alertness** Simple RT **Selective Attention** Ruff 2&7 Test **Memory span** Digit span **Visual memory** Benton Revised Visual Retention Test **Visual memory** Rey complex Figure Test **Procedural Memory** Finger Tapping **Learning** Auditory Verbal Learning Test **Inhibition** Stroop Test **Set-Shifting** Trail Making Test A-B **Flexibility** Paced Auditory Serial Addition Test **Fluency**	***Neuroimaging*** Structural Magnetic Resonance Imaging (MRI) Single Photon Emission Tomography (SPECT)	N/A

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Table 1 (*continued*)

Reference	Sample	Mean age	Age at onset	Treatment	Cognitive Measures	Other Measures	Procedure
					F-A-S test **Intelligence** WAIS-R, WISC-III		
Mazzetti [36] 2006 Italy	15 Narcolepsy with Cataplexy (ICSD-2) 15 healthy controls	31.25 ± 3.19 30.92 ± 3.89	N/A	drug naïve	**Declarative Memory** Memory Quotient (WMS) **Procedural Memory** Lexical Decision Task **Reasoning** Baddeley's Logical Reasoning **Set-Shifting** Trail Making Test A-B **Intelligence** WAIS-R	**Sleepiness** ESS ***Depression*** BDI	Three experimental sessions: training, 1st-d retrieval and 7th-d retrieval
Mazzetti et al. [39] 2010 Italy	16 Narcolepsy with Cataplexy (ICSD-2) 16 healthy controls	29.69 ± 4.56 29.87 ± 5.2	N/A	drug naïve	**Declarative Memory** Memory Quotient (WMS) **Reasoning** Baddeley's Logical Reasoning **Set-Shifting** Trail Making Test A-B **Intelligence** WAIS-R	**Sleepiness** ESS	N/A
Mazzetti et al. [40] 2012 Italy	14 Narcolepsy with Cataplexy (ICSD-2) 14 healthy controls	31.36 ± 8.41 30.86 ± 7.14	N/A	drug naïve	**Declarative Memory** Memory Quotient (WMS) **Procedural Memory** Finger Tapping **Reasoning** Baddeley's Logical Reasoning **Set-Shifting** Trail Making Test A-B **Intelligence** WAIS-R	**Sleepiness** ESS	Three experimental sessions: training, 1st-d retrieval and 7th-d retrieval
Medrano-Martinez et al. [29] 2020 Spain	30 Narcolepsy Type 1 (ICSD-3) 28 healthy controls	40.9 ± 12.4 40.9 ± 12.5	22.3 ± 9.5	10 drug naïve (one month)	**Complex Attention Measure** Test for Maintenance of Attention **Memory Span** Digit and Arithmetic Tests **Inhibition** Stroop test **Set-Shifting** Trail Making Test A-B **Planning** Zoo Map Test **Fluency** F-A-S test	***Sleepiness*** ESS ***Anxiety-Depression*** BDI-II STAI	Neuropsychological testing was performed in the morning (10:00−13:00 AM) Participants completed the ESS prior to performing the neurophysiological test
Moraes et al. [32] 2012 Brazil	19 Narcolepsy with Cataplexy (ICSD-2) 19 healthy controls	37.58 ± 8.93 34.42 ± 12.31	N/A	16/19 with stimulant and antidepressant	**Working Memory** Digit And Arithmetic Tests **Inhibition** Victoria Stroop Test **Set-Shifting** Trail Making Test A-B	***Sleepiness*** ESS ***Socioeconomic status*** Brazil Economic Classification	N/A
Naumann et al. [15] 2001 Germany	12 Narcolepsy with Cataplexy (ICSD-2) 12 healthy controls	41.3 ± 16.1 41.5 ± 16.7	16 ± 10.1	15/15 treatment not specified	**Attentive and Pre-attentive Processes**	***Sleepiness*** SSS	N/A

					Passive Auditory Task Auditory Odd-Ball Task	***Neurophysiological*** ERP P3, MMN	
Naumann at al. (Study 1) [10] 2006 Germany	15 Narcolepsy with Cataplexy (ICSD-2) 15 healthy controls	38.3 ± 15.9 38.8 ± 16.2	19.1 ± 14.5	11/15 treated with Ritalin or Vigil	**Alertness** Simple/Forewarned RT **Selective Attention** d2 Test **Divided Attention** Divided attention test **Working Memory** 2-Back Task **Flexibility** incompatibility test **Memory Span** Digit Span	***Sleepiness*** SSS VAS	Participants were let free to choose the time of day at which they felt at their optimal cognitive functioning and were tested individually in a 1.5 h session. After 45 min participants have a 10 min planned break.
Naumann et al. (Study 2) [10] 2006 Germany	21 Narcolepsy with Cataplexy (ICSD-2) (12 participated in study a) 21 healthy controls	35.9 ± 12.7 36 ± 13.2	15.3 ± 10.4	15/21 treated (treatment not specified)	**Declarative memory** Immediate/delayed recall (WMS-R) **Verbal Memory** Structured 16-item word lists recall Task **Visual memory** Benton Revised Visual Retention Test **Reasoning** Hayling Sentence Completion Test **Fluency** Verbal fluency Test (country name/N-nouns/ male first name/vegetables)	***Sleepiness*** SSS VAS	Participants were let free to choose the time of day at which they felt at their optimal cognitive functioning and were tested individually in a 1.5 h session. After 45 min participants have a 10 min planned break.
Park et al. [34] 2016 South Korea	22 Narcolepsy with Cataplexy (ICSD-2) 26 healthy controls	26.9 ± 7.9 30.1 ± 11.1	N/A	either drug naïve or drug free (not specified)	**Complex Attention** **Measure** Digit symbol test **Memory Span** Digit Span forwards/ backwards **Visual memory** Rey complex Figure **Working Memory** Corsi Block Tapping Test **Inhibition** Stroop Test **Set-Shifting** Trail Making Test A-B **Fluency** Controlled Oral Word Association Test **Learning** Korean California Verbal Test	***Sleepiness*** MSLT ***Anxiety-Depression*** BDI ***Neuroimaging*** Structural magnetic resonance imaging	Participants were tested individually in a 2.50 h session. Information on times and procedures of MRI scan are not reported
Ponz et al. [50] 2010 Switzerland	12 Narcolepsy with Cataplexy (ICSD-2) 12 healthy controls	30.5 ± 7.98 32 ± 7.43	13.25 ± 8.13 (dd)	drug naïve	**Reward Process** Monetary Incentive Delay Task	***Sleepiness*** ESS SSS Ullanlinna Swiss–Narcolepsy Scale Stanford Cataplexy Scale ***Anxiety-Depression*** BDI STAI ***Neuroimaging*** fMRI	Information on times and procedures of MRI scan are not reported

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Table 1 (*continued*)

Reference	Sample	Mean age	Age at onset	Treatment	Cognitive Measures	Other Measures	Procedure
Ponz et al. [51] 2010 Switzerland	9 Narcolepsy with Cataplexy (ICSD-2) 9 healthy controls	33.78 ± 8.36 34.66 ± 8.15	13.44 ± 7.95 (dd)	drug free (for at least one month)	**Reward Process** Triangle-Orientation Task	***Sleepiness*** ESS SSS Ullanlinna Swiss—Narcolepsy Scale Stanford Cataplexy Scale ***Anxiety-Depression*** BDI STAI ***Neuroimaging*** fMRI	Participants performed the Triangle-Orientation Task coupled with brief painful electrical stimulation (aversive conditioning paradigm) during fMRI scanning
Ramm et al. [7] 2018 Germany	9 Narcolepsy type 1 (ICSD-3) 3 Narcolepsy Type 2/11 Idiopathic Hypersomnia (ICSD-3) 13 Subjective Hypersomnia 20 healthy controls	N/A N/A 32.2 ± 14.6 32.6 ± 11.3	N/A N/A N/A	N/A N/A N/A	**Alertness** Simple/Forewarned RT **Selective Attention** Selective attention test **Divided Attention** Divided attention test **Sustained Attention and Vigilance** Sustained attention test Vigilance test	***Sleepiness*** ESS MSLT MWT **Fatigue** Fatigue severity scale ***Depression*** BDI ***Sleep Quality*** PSQI	Experimental session was performed in the morning (9:00 −13:00)
Ramm et al. [19] 2019 Germany	10 Narcolepsy type 1 (ICSD-3) 14 Idiopathic Hypersomnia (ICSD-3) 14 Subjective Hypersomnia 20 healthy controls	26.7 (20.0—33.49 33.6 [26.8—40.4] 31.4 [23.1—39.7] 32.6 [27.3—37.9]	N/A N/A N/A	drug free drug free drug free	**Selective Attention** Selective attention Test **Sustained Attention and Vigilance** Vigilance test	***Sleepiness*** ESS **Fatigue** Fatigue severity scale ***Depression*** BDI ***Sleep Quality*** PSQI	Participants were tested individually in a 90 min session.
Reiss et al. [49] 2008 USA	10 Narcolepsy with cataplexy (ICSD-R) 10 healthy controls	29.8 ± 6.5 25.9. ± 4.1	N/A	drug free	**Emotional Process** Humour judgement paradigm	**N/A**	Subjects received 70 stimuli (30 humorous and 40 non-humorous cartoons), Task duration was 15 min and 4 s.
Rieger et al. [12] 2003 Germany	19 Narcolepsy (ICSD-R) 20 healthy controls	39.9 ± 16.1 40.1 ± 13.3	10.4 ± 10.7 (dd)	13/19 drug naïve	**Alertness** Simple/Forewarned RT **Selective Attention** Visual scanning **Divided Attention** Dual task **Flexibility** Alternating reactions **Learning** Auditory verbal learning test	***Sleepiness*** ESS SSS	NT1 patients were tested individually (10 min) after the first MSLT session at 9:00
Saletu et al. [16] 2008 Austria	17 Narcolepsy (ICD-10) 17 healthy controls	38.2 ± 19 39 ± 19	N/A	drug free	**Attentive and Pre-attentive Processes** Auditory Odd-Ball Paradigm **Selective Attention** Psychomotor Activity Test **Verbal Memory** Grünberger Verbal Memory Test	***Sleepiness*** ESS VAS MSLT **Anxiety** STAI ***Neurophysiological*** ERP N1, P1, N2, P3, low-resolution electromagnetic tomography	N/A

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Schneider et al. [20] 2004 Germany	10 Narcolepsy (ICSD-R) 10 untreated obstructive sleep apnea (ICSD-R) 10 obstructive sleep apnea treated with CPAP (ICSD-R) 10 Psychophysiological Insomnia 10 Healthy Controls	53.1 ± 11.6 54.8 ± 8 53.3 ± 11.8 50.7 ± 10.1 51.5 ± 9.5	N/A N/A N/A N/A	All on anticataplectic drug free drug free drug free drug free	**Selective Attention** Visualization Subtest (Repetitive Psychometric Tests Series, RPM-V)	***Sleepiness*** ESS VAS MSLT **Fatigue** Tiredness Symptoms Scale ***Depression*** BDI ***Neurophysiological*** Critical flicker fusion test	Neuropsychological evaluation lasted for 10 h (08:00–18:00). Tests were administered at 20 min intervals. Task Order: CFF test (3 min) RPM-V (3 min)
Schwartz et al. [48] 2008 Switzerland	12 Narcolepsy with Cataplexy (ICSD-2) 12 healthy controls	32.8 5 ± 8.25 33.83 ± 6.90	13.25 ± 8.18 (dd)	drug free (14 days)	**Emotional Process** Humour judgement paradigm	***Sleepiness*** ESS MSLT Ullanlinna Swiss–Narcolepsy Scale Stanford Cataplexy Scale ***Neuroimaging*** fMRI	The task was performed during fMRI scanning
Thomann et al. [25] 2014 Switzerland	20 Narcolepsy with Cataplexy (ICSD-2) 67 Insufficient Sleep Syndrome (ICSD-2) 56 Hypersomnia Disorders Of Other Origin (ICSD-2) 67 healthy controls	37 ± 17 40 ± 14 43 ± 15 42 ± 17	N/A N/A N/A	drug naïve drug naïve drug naïve	**Sustained Attention and Vigilance** Psychomotor Vigilance Task **Driving Simulation** Steer Clear Test	***Sleepiness*** ESS MWT	The task was administered twice a day (morning and afternoon hours). Data analyzed are the mean of the two sections
Tucci et al. [45] 2003 Italy	8 Narcolepsy with Cataplexy (ICSD-2) 8 healthy controls	36.5 ± 18.94 31.75 ± 14.19	N/A	drug naïve/drug free	**Emotional Process** Humour judgement paradigm	***Neurophysiological*** ERP N2 e P3	Patients with were tested at 8:00
Uguccioni et al. [54] 2016 France	122 Kleine-Levin Syndrome (ICSD-2) 42 healthy controls	21.5 ± 9 22. 5 ± 8.5	N/A	drug naïve (36/42 treated at the second assessment)	**Memory Span** Digit Span forwards/ backwards **Declarative memory** Free and Cued Selective Reminding Test **Visual memory** Rey complex Figure Test **Working Memory** Working Memory Task **Set-Shifting** Trail Making Test A-B **Inhibition** Stroop Test **Fluency** Verbal fluency Test (M-words/P-words)	***Sleepiness*** ESS ***Anxiety-Depression*** HADS ***Chronotype*** Morning-Eveningness Questionnaire	Forty-four patients underwent a second assessment at 1.7 ± 1.0 y after the first visit All patients were tested in an asymptomatic period
Van Holst et al. [33] 2018 Netherlands	23 Narcolepsy Type 1 (ICSD-3) 15 Idiopathic Hypersomnia (ICSD-3) 20 healthy controls	33.83 ± 8.36 36.20 ± 12.89 36.75 ± 12.14	8.17 ± 8.29 (dd) 6.40 ± 8.13 (dd)	drug free (at testing)	**Memory Span** Digit Span **Inhibition** Stroop Test Food Stroop Test	***Sleepiness*** ESS ***Sleep Quality*** PSQI ***Eating disorder*** Eating Behavior Questionnaire ***Neuroimaging*** fMRI	fMRI session lasted about 45–60 min and was performed in the late morning (9:00–13:00)

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Table 1 (*continued*)

Reference	Sample	Mean age	Age at onset	Treatment	Cognitive Measures	Other Measures	Procedure
Van Schie et al. [22] 2012 Netherlands	42 Narcolepsy with Cataplexy (ICSD-2) 5 Narcolepsy without Cataplexy (ICSD-2) 37 Idiopathic Hypersomnia (ICSD-3) 12 obstructive sleep apnea (ICSD-2)	37.5 ± 19.1 43.8 ± 20.3 44.2 ± 15.0 57.4 ± 14.5	N/A N/A N/A N/A	drug free (at testing) drug free (at testing) drug free (at testing) N/A	**Sustained Attention and Vigilance** Sustained Attention to Response test (SART)	***Sleepiness*** MSLT	The SART was administered five times, prior each MSLT sessions.
Van Schie et al. [23] 2016 Netherlands	26 Narcolepsy with Cataplexy (ICSD-2) 12 healthy controls	34.8 34.1	N/A	drug naïve	**Sustained Attention and Vigilance** Psychomotor Vigilance Test (PVT) Sustained Attention to Response test (SART)	***Sleepiness*** SSS	Patients and controls underwent a 9-day protocol consisting of: 2-day in-laboratory assessment (SART and PVT was administered three times in the day at 10:00, 14:00 and 20:00) 7-day in-field assessment: out-of-hospital tasks were administered at the same time windows through a portable device.
Witt et al. [35] 2018 Sweden	17 Narcolepsy type 1 (ICSD-2) 20 healthy controls	16.5 ± 1.9 17.4 ± 2.6	3.7 ± 1.2 (dd)	15/17 on stimulants	**Memory Span** Digit span forward Listening span **Working Memory** Working Memory Task **Visual memory** Rey complex Figure Test **Set-Shifting** Trail Making Test (A-B)	***Neuroimaging*** fMRI	The working memory test (delayed recall of sequences from the reading span task) was performed during fMRI scanning
Yoon et al. [30] 2013 South Korea	33 Narcolepsy with Cataplexy (ICSD-2) 33 healthy controls	29.9 ± 12.7 30.1 ± 12.7	16.4 ± 11.4	drug naïve	**Complex Attention Measure** Digit symbol test **Memory Span** Digit Span forwards/ backwards **Visual memory** Rey complex Figure **Working Memory** Corsi Block Tapping Test **Inhibition** Stroop Test **Set-Shifting** Trail Making Test A-B Wisconsin Card Sorting Test **Fluency** Controlled Oral Word Association Test Boston Naming Test **Learning** Korean California Verbal Test **Reasoning** Raven's colored Progressive Matrices	***Sleepiness*** ESS MSLT ***Depression*** BDI	N/A
Zamarian et al. [17] 2015 Austria	51 Narcolepsy with Cataplexy (ICSD-2) 35 healthy controls	38.94 ± 14.15 39.86 ± 13.96	22.37 ± 8.70	35/51 on treatment (68% with stimulants)	**Selective Attention** d2 Test **Memory span** Digit span forwards/	**Sleepiness** ESS SSS	Participants were tested in the morning for 60 min. Participants were invited to

backwards	MSLT	take a break if they felt sleepy.
Learning	**Self-Evaluation Attention**	
Auditory Verbal Learning Test	Subjectively deficits of attention questionnaire	
Inhibition	***Anxiety-Depression***	
Go-NoGo	HADS	
Set-Shifting		
Intra/Extra Dimensional Shift		
Planning		
One Touch Stockings of Cambridge		
Fluency		
Verbal fluency Test (Animals/S-words/Fruits-sports)		

Abbreviations: dd – diagnostic delay; years; SSS – Stanford sleepiness scale; ESS – Epworth sleepiness scale; MSLT – Multiple sleep latency test; MWT – Maintenance of wakefulness test; HADS – Hospital anxiety and depression scale; BDI – Beck depression inventory; fMRI – functional magnetic resonance imaging; PSQI – Pittsburgh sleep quality index; STAI – State-trait anxiety inventory; ERP – Event-related potential; MMN – Mismatch negativity; WAIS-R – Wechsler Adult Intelligence Scale revised; WMS – Wechsler memory scale; PDSS – Pediatric daytime sleepiness scale; VAS – visual analogue scale; UPPS – Urgency; premeditation; perseverance; sensation seeking; positive urgency; impulsive behavior scale; PET – Positron emission tomography; ICSD-2– international classification of sleep disorders second-edition; ICSD-3– international classification of sleep disorders third-edition.

differences in any of SART measures but a high error rate in all groups [22].

In a later study, Van Schie administered the SART and the psychomotor vigilance task (PVT) to NT1 and controls at specific times of day [23]. NT1 patients made more errors on SART and had slower RTs on PVT than controls, regardless of time windows. Two other studies adopted PVT. Dimitrova reported slower RTs in NT1 than controls, but did not report/analyze errors [24]. Thomann administered the PVT to NT1, ISS patients, controls and patients suffering from hypersomnia disorders of other origin. NT1 patients showed slower and more variable RTs and increased omission errors relative to ISS patients and controls [25].

Huang assessed vigilance in NT1, NT2 patients and controls within a positron emission (PET) examination protocol. Subjects received the F-fluorodeoxyglucose (FDG) injection and performed the CPT. PET scan was performed 30 min after injection [26]. No group differences were observed in omission, commission and overall error rate but NT1 patients presented higher CPT clinical confidence index (summary score of CPT subsections, with higher scores indicating performance closer to a clinical profile) and response style T score (cautiousness in avoiding commission errors) than controls and slower and more variable RTs than controls and NT2 patients. NT1 patients presented hypermetabolism in several brain areas (fusiform gyrus, striatum, hippocampus, thalamus, basal ganglia, and cerebellum) and hypometabolism in the frontal lobe, posterior cingulum, angular gyrus and parietal lobe compared to controls. In NT1 patients, hypometabolism over frontal and parietal areas was associated with fewer errors on CPT. Total sample assessed: 290 NT1 compared to 49 NT2, 65 IH, 13 subjective EDS, 12 OSAS, 67 ISS, 56 hypersomnia disorders of other origin and 226 healthy controls.

Driving simulation

Kotterba administered the computer aided risk simulator test reporting that NT1 patients had more crashes with obstacles and off-road driving compared to controls [11]. Two studies used the Steer Clear test. Thomann reported more collision in NT1 compared to ISS patients [25]. Poryazova administered the Steer Clear to NT1 patients before and after a treatment with sodium oxybate reporting a reduction of collisions after two years of stable treatment [27]. Total sample assessed: 50 NT1 compared to 67 ISS, 56 hypersomnia disorders of other origin and 77 healthy controls.

Complex attention measures

Filardi administered the attention network test assessing in parallel the alerting, orienting and executive control network of NT1, NT2 patients and controls [28]. NT1 patients displayed slower RTs than controls, and abnormal alerting network functioning compared to NT2 and controls. No differences emerged for the orienting and executive control network. Medrano-Martinez administered three attentional tasks with increasing difficulty [29]. NT1 displayed slower RTs but intact quality of performance on the simple RTs task, while on the multiple and complex RTs tasks, NT1 displayed slower RTs and made errors than controls. Two studies used the digit symbol substitution test: Yoon reported impaired performance in NT1, while Kim reported no difference between NT1 and controls [30,31]. Sample assessed: 115 NT1 compared to 15 NT2 and 114 healthy controls.

Summary

NT1 patients show reduced performance in most of the attentional functions investigated.

Regardless of the adopted task or the specific aspect of attention assessed, NT1 patients display slower and more variable RTs and a rapid decline of performance over time-on-task.

Table 2
Description of neuropsychological tasks.

	Description	Duration	Test battery	Outcomes
ALERTNESS				
Simple and forewarned reaction time [7,10,12,13]	Two conditions: tonic and phasic. In tonic condition only the visual stimulus is presented. In phasic condition, an auditory warning signal is presented before the visual stimulus.	5–10 min	TAP/WAF	RTs, RTs variability (SD), RTs variability across blocks, alerting reaction (RTs tonic - RTs phasic)
Simple reaction time [11,53]	Reaction task on visual stimuli.	5 min	VTS	
Reaction unit test [14]	Reaction task with different stimulation modalities: visual, auditory, and audiovisual.	10 min	VTS	
SELECTIVE ATTENTION				
Visual Scanning test [12]	Subjects have to decide whether target stimulus (a square, open on top) is absent or present in a 5 by 5 matrix of squares.	10 min	TAP	Time needed to complete the test, stimuli correctly processed, search strategies adopted, errors, lapses
"d2" Attention Test [10,17,19]	Subjects have to mark all letters "d" with two marks (around, above or below it) among distractors similar to the target.	4–5 min		
Ruff 2–7 Test [53]	A number-cancellation task. In half of trials the target numbers are presented among distractor letters; in the other half of trials the target numbers are presented among distractor numbers.	7–10 min		
Selective attention task [7,19]	Various geometric stimuli (i.e., circle, square and triangle) are presented; subjects have to respond to a predefined stimulus condition while ignoring other stimuli.	8 min	WAF	
Grünberger's Psychomotor Activity Test [16]	Subjects have to place dots in small boxes within 15 s.	8–10 min		
Repeated psychometric measures, visualization subtest [20]	Several set of 10 tangled lines are presented, lines starting point are numbered. Subjects have to track one line after the other and place line number into the appropriate cells.	3 min		
DIVIDED ATTENTION				
Dual task [10,12]	Two conditions: visual and auditory. In the visual task, a display of 16 points is presented; subjects have to respond when four of those cross a small square. In the auditory task, alternating sequence of high and low tones are presented; subjects have to respond when detecting an irregularity in the sequence. Three blocks: a) visual only; b) auditory only and c) visual and auditory together.	11 min	TAP	Errors rate, errors at dual-task condition, errors at dual-task condition compared to single-task condition, RTs
Divided and continuous attention test [11]	Subjects have to respond when the target stimulus flashes and, in parallel, react to acoustical stimulus by pressing a foot pedals.	12–30 min	WAF	
Divided attention test [7]	Subjects have to respond when one of the two stimuli (a grey square or an auditory signal) changes in intensity twice in succession.	8 min	WAF	
SUSTAINED ATTENTION AND VIGILANCE				
Vigilance Test [11,14]	Subjects have to react on when the target stimulus (a beam going up and down) has higher swings.	25–30 min	TAP	Omission error, commission error, error rate, CPT confidence index, CPT response style, detectability, variability and perseverations score, RTs
Vigilance/sustained attention test [7,19]	Subjects have to respond to changes in the intensity of the color of a black square (discriminative stimuli). In vigilance task the discriminative stimulus appears in 5% of total trials; in sustained attention task the rate of discriminatory stimuli is 30% of total trials.	30 min (each test)	WAF	
Sustained Attention to Response Task [21–23]	Subjects have to respond to the appearance of the target stimuli (numbers 1–9 in random order) except when the number is 3.	4.20 min		
Psychomotor Vigilance Task [23–25]		10 min		

Table 2 (*continued*)

	Subjects have to respond when the target stimulus (a light) appears on the screen.			
Continuous performance test [14,26]	Subjects have to respond when a letter other than X appears on the screen.	14–20 min		
DRIVING SIMULATION				
Computer Aided Risk simulator [11]	Sit in the simulator, subjects have to drive on a highway maintaining a mean speed of 100 km/h. Different weather and daytime conditions are presented in random order.	60 min		Accidents (crashes and off- road driving), concentration lapses
Steer Clear test [25,27]	Subjects have to avoid hitting the obstacles (steers) by moving an automobile from one to the other lane of highway.	30 min		
COMPLEX ATTENTION				
Alerting network test [28]	Simultaneous assessment of three attention components: alerting, orienting, and conflict processing.	20 min		RT, RTs variability, alerting, orienting and executive network scores, errors.
Computerized assessment of maintenance of attention [29]	Three tasks with different level of complexity. Simple response: subjects are presented with a circle formed of small moving circles and they have to react when the circle advanced two positions instead of one; multiple response: subjects have to press different button depending on the location of the target stimulus (four spatial positions); complex response: subjects have to react only when a three-digit number is composed entirely of odd or even numbers.	15 min		
Digit symbol substitution test [30,31]	A series of numbers from 1 to 9 each paired with a unique symbol. Subjects have to write the correct symbol for each number.	2 min		
MEMORY SPAN				
Digit Span [10,17,18,30,31,33–35,53–55]	Two conditions: forward and backward. In forward condition, subjects have to repeat numbers in the same order as presented. In backward condition, subjects have to repeat numbers in the reverse order as presented.	16 min	WAIS	Forward digit span score, backward digit span score, longest forward digit span, longest backward digit span, listening span score, arithmetic score.
Listening span [35,55]	Subjects listen sequences of letters (3–7 letters) that have to be recalled it in the correct order.	20 min	WAIS	
Arithmetic span [29]	Subjects have to resolve a series of arithmetic questions.	15–20 min	WAIS	
DECLARATIVE MEMORY				
Wechsler Memory Scale [37–41]	A neuropsychological assessment battery composed of seven subtests assessing multiple aspects of learning and memory.	30–35 min		Errors, memory quotient, general verbal memory score, associative verbal memory score, numerical memory score, total verbal memory score, Rey complex figure total score, copy score, immediate recall score, delayed recall score, recognition score, errors.
Rey complex figure [36–40]	Subjects have to reproduce a complicated drawing by copying it freehand (recognition), and then drawing it from memory (recall).	30–45 min		
Immediate/delayed recall of a prose passage and structured word lists [10,54]	Subjects have to recall a prose passage and three structured 16-item word lists.	30 min		
Benton visual retention test [10,53]	Different geometric patterns, each composed by one or more figures are presented for 10 s. Subjects are asked to have to draw the figures from memory immediately after presentation.	10–15 min		
Grünberger's verbal memory test [16]	Three subtests. General verbal memory: subjects are told three stories, each including four items that they have to recall; associative verbal memory: subjects have to repeat 10 groups of three associative items and to reproduce the other two associative words on the presentation of the first cue word; numerical memory: subjects have to recall a list of numbers.	30–45 min		

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Table 2 (*continued*)

PROCEDURAL MEMORY				
Visual texture discrimination task [38]	Three sequential displays are presented: 1) a fixation point; 2) a rotated letter (T or V) at the fixation point and a array of three diagonal bars (horizontally or vertically arranged) in the upper left quadrant and 3) a blank inter-stimulus interval followed by exposure to mask. Subjects have to indicate which letter was presented at the fixation point and whether the array of three diagonal are arranged horizontally or vertically.	50 min		Errors, performance improvement across sessions, semantic priming effect
Lexical decision task [36]	A fixation point appeared followed by a prime and immediately after by a target word. Subjects are asked to read respond when the target word is a real word and to avoid responding when the target word is a pseudoword.	2.5 min		
Finger-tapping test [40,53]	Subjects have to press repeatedly a sequence of five elements (6-3-5-4-6) with the fingers of the non-dominant hand.	15 min		
WORKING MEMORY				
Corsi block-tapping test [14,30,31,34]	Subjects have to tap a series of block, reproducing a sequence of spatial positions of increasing length.	5–10 min		Errors, maximum memory capacity, longest remembered sequence, CBTT forward and backward score
2-back test [10,13]	Subjects have to decide whether the current stimulus matches the one displayed two trials before.	10 min		
Work performance series [14]	Subjects have to carry out additions or subtractions of two numbers, the lower number is concealed each time they answer and must be memorized to perform the next operation.	10 min	VTS	
Reading span task [35,55–57]	Subjects have to evaluate whether sentences (in blocks of one, three or five) make sense or not and memorize the last word. After a variable delay, subjects are presented with four words and have to indicate, for each word, whether it was presented in the immediately preceding block.	12.45 min		
Letter-number sequencing [32]	Subjects have to remember a string of digits and letters and then repeat numbers in chronological order and letters in alphabetical order.	8–10 min	WAIS	
LEARNING				
California verbal learning test [30,31,41]	Two words lists and a recognition task. The first list includes 16 items from four semantic categories; subjects have to recall as many words as possible. The second list shares two categories with the first list and has two unshared categories. In the recognition task subjects have to indicate whether an element, in a 44-word list, is a target word or a distractor.	40–50 min		Number of items recalled (first list and second list), number of words from the first list recalled after the disruption by the second list, items recalled at the recognition test, CVLT and AVLT total score
Auditory verbal learning test [12,17,53]	Two word lists (15 words each). Subjects have to remember and repeat as many words as possible from the first and the second list. In the last part subjects are presented with 50 words, consisting of the words of the two lists plus semantically and/or phonetically similar words, and have to decide which of those words belong to the first list.	40–50 min		
INHIBITION				
Go/No-go task [13,17,18,53]	Subjects have to respond when the target stimulus indicate “Go” and not to respond when the target stimulus indicate “No-Go”.	7–10 min		Errors, commission errors, Stroop interference index, RTs for response initiation and inhibition, RTs difference between congruent and incongruent trials, percentage of subjects
Stroop test [30,34,53]	Color words printed in different colours of ink are presented; subjects have to respond as quickly as possible according to the color of the ink rather than the written word.	5 min 5 min		

Table 2 (*continued*)

Stroop color and word test [29,31,54]	Three tables are presented. A table of color words printed in black, a table of "X" printed in color and a table containing words from the first table printed with color from the second table. Subjects have to read words or name the ink color as quickly as possible.			performing at ceiling, RTs
Victoria Stroop test [32]	Three parts. In the first part subjects have to name the color of 24 rectangles. In the second one subjects have to name color words. In the third part subjects have to name color words not matching their meaning.	5 min		
Food Stroop test [33]	Different words (unhealthy/healthy foods, animal names, and color words) printed in four different color are presented; subjects have to respond to the color of the words.	5 min		
Hayling Sentence Completion Test [10]	Thirty sentences with the last word omitted are presented. In the first 15 sentences subjects have to complete the sentence with the obvious ending. In the second 15 sentences subjects are asked to complete the sentence with unrelated word.	5 min		
SET-SHIFTING				
Trail making test [29–32,35–40,53,54]	Two subtests (TMT-A and TMT-B). In TMT-A, subjects have to connected the circled numbers in numerical order (from 1 to 8). In TMT-B, subjects have to connect the circled numbers alternating numbers and letters in progressive order (i.e., 1-A, 2-B, 3-C).	5–10 min	CANTAB	TMT-B completion time, switch cost (TMT-B minus TMT-A), number of completed stages, trials needed to complete a stage, WCST errors, perseverative errors and perseverative response score.
Intra/extra dimensional shift [17,18]	Subjects have to learn a series of two alternative forced-choice discriminations using the feedback provided by the computer. After six correct responses the stimuli and/or rules changes.	5–8 min		
Wisconsin Card Sorting Test [26,30]	Subjects have to sort 64 cards based on color, form, or number of figures. During the task, the sorting rule changes without the subjects being informed. Subjects have to sort cards following the new sorting rule.	20–25 min		
PLANNING				
One touch stockings of Cambridge test [17,18]	Three colored balls attached by a beam are presented in the upper display. Subjects have to figure out how many moves are necessary to copy the pattern of the upper display and indicate the correct response.	10 min	CANTAB	Number of problems solved at first choice, number of choices to a correct response, mean latency to the correct choice, Zoo map test completion time and total score.
Zoo map test [29]	Subjects have to plan a route to visit 6–7 of a possible 12 locations in a zoo. They are required to follow several rules when planning the route (e.g., visit only certain animals/places and walking along each path only once).	10 min		
FLEXIBILITY				
Incompatibility test [10]	Arrows are presented on the left or the right side of a fixation point on a screen. Subjects have to press the left or right response key according to the direction of the arrowhead while ignoring its spatial location.	10 min	TAP	Errors, errors in compatible trials relative to incompatible trials, errors in "same hand" response condition relative to "other hand" response condition, RTs.
Cognitrone [14]	Subjects have to compare an abstract figure with a model and decide if the two are identical. Six test forms have no time limit and two forms have a 1.8 s time limit per item. Test forms have increasing complexity.	5–20 min	VTS	
Determination unit task [14]	Color stimuli and acoustic signals are presented. Three different presentation modes: adaptive mode (the presentation speed is adjusted	15 min	VTS	

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Table 2 (*continued*)

	according to the performance of the subject) action mode (no time limit) and random mode (fixed time limit)			
Flexibility task [13]	A letter and a digit are presented on the left or right side of the display. Subjects have to indicate the side where the digit or the letter is presented responding alternatively to the letter or digit location.	5–7 min	TAP	
Alternating reactions [12]	Two stimuli a letter and a number are simultaneously presented on the left and right of the display. Subjects have to indicate the side on which the critical stimulus (which is alternately the letter or number) appears. In half of trials subjects have to respond with the same hand as the previous trial; in the other half of trials subjects have to respond with the other hand.	5–10 min	TAP	
Paced auditory serial addition test [53]	Subjects have to add each number to the one immediately preceding it.	10 min		
REASONING				
Baddeley logical reasoning test [36–40]	Statements like "A follows B" paired with 2 letters "AB" or "BA" are presented. Subjects have to judge whether the sentence is a correct representation of the letter pair which follows it.	3 min		Errors, tasks total score
Raven's progressive matrices [14,30]	Subjects have to establish the pattern linking a series of figures, indicating the desired figure among the six proposed options.	15–30 min		
Hypothesis formation [14]	Subjects have to judge whether the sentence is appropriate. Difficulty increase across trials (i.e., simple, moderate, complex).	15–20 min		
DECISION-MAKING				
Iowa gambling task [18,43,44]	Subjects must draw a card from one of the four decks of cards and win as much money as possible. Two decks have higher short-term reward but over time are disadvantageous; two decks have low immediate payoffs but over time are advantageous.	15–30 min		Boxes opened, probability of being correct at the point of decision, number of pumps, mean pumps/ balloon, balloons exploded, trials in which subjects continued to select advantageous choice despite negative feedback, trials in which subjects shifted from disadvantageous to advantageous decks after negative feedback, IGT net score (advantageous minus disadvantageous card selections).
Game of dice task [43,44]	Subjects are instructed to maximize their starting capital of 1000€ within 18 dice throw. Subjects have to bet on the outcome by choosing between single numbers or a combination of 2, 3 or 4 numbers. Each choice is associated with different gains or losses depending on the probability of occurrence.	5 min		
Information sampling task [18]	A 5 × 5 matrix of gray boxes are presented, selecting the box reveal one of two colors (boxes remain open through the trial). Subjects have to decide which color is inside the majority of boxes; they can open as many boxes as they wish before making the decision.	10–15 min		
Balloon analogue risk task [24]	Thirty balloons are presented, each with a different explosion point. Subjects have to pump the balloons, with each pump they earn money but if the balloon explodes before they collect the winnings they lose all money. Subjects can decide to end the trial at any time and bank the money accumulated.	6–8 min		
CREATIVITY				
Evaluation of Potential Creativity [52]	Two tasks. In divergent-exploratory task, subjects have to generate as many alternative ideas as possible based on stimulus, i.e., inventing as many different endings of one story or generating as many different drawings as possible incorporating one shape or object. In convergent-integrative task, subjects have to create a story that	120 min		Divergent-exploratory score (originality, fluency, flexibility), convergent-integrative score (accuracy, response time)

Table 2 (*continued*)

	incorporates three main characters (imposed) or producing one original drawing that incorporates a set of forms or objects.		
FLUENCY			
Controlled oral word association/F-A-S test [10,17,18,29–31,34,53,54]	Subjects have to produce as many words as possible from different categories: semantic (i.e., nouns of animals), phonemic (i.e., nouns beginning with the letters F, A, or S) and in alternation.	3–5 min	Semantic words per minute, F-A-S words per minute, alternation words per minute, correct responses,
Boston naming test [30]	Subjects have to name line drawings of objects with increasing naming difficulty. If a response is not made after 20 s, two cues (phonemic or semantic) are provided.	20 min	responses after phonemic/semantic cues.

TAP: Testbatterie zur Aufmerksamkeitsprüfung (Zimmermann and Fimm's test battery).
WAF: Perception and Attention Functions test battery.
VTS: Vienna Test System.
WAIS: Wechsler Adult Intelligence Scale.
CANTAB: Cambridge Neuropsychological Test Automated Battery.

Box 1
Cognitive functions assessed in CDH patients.

Alertness

Alertness refers to the ability to increase the attentional level when a stimulus of high priority is likely to appear. Alertness tasks usually comprise two conditions: tonic and phasic.
In the tonic condition only the target stimulus is presented, in the phasic condition a warning signal is presented shortly prior to the target stimulus. The alertness reaction is calculated as the difference between these conditions ($RTs_{\text{tonic condition}} - RTs_{\text{phasic condition}}$).

Selective attention

Selective attention describes the ability to prioritize the information processing of specific stimuli while suppressing responses to irrelevant stimuli. Selective attention task usually requires subjects to mark all target stimuli (letters, numbers or various geometric forms) among different distractors as fast and accurately as possible.

Divided attention

Divided attention refers to the ability to direct awareness toward more than one task at the same time. Two different stimuli are presented simultaneously and through more than one sensory modality (e.g., acoustic and visual). In divided attention tasks the target stimuli are presented first individually (single-task condition) and then concurrently (dual-task condition).

Sustained attention and vigilance

Sustained attention and vigilance refer to the ability to respond to rarely and irregularly occurring stimuli. Sustained attention describe the ability focus on tasks over extended periods of time; vigilance describe the ability detect infrequent and unpredictably occurring stimuli over prolonged periods of time.

Memory span

Memory span refers to the ability to repeat back, after a single presentation, a list of stimuli in the correct order. Memory span is evaluated for different lists of stimuli (words, letters, and numbers) and through different presentation modalities (reading, listening). Subjects are asked to repeat the longest list of items they could in the given order (forward span) or in reverse order (backward span).

Declarative memory

Declarative memory (explicit memory) refers to the memory system dedicated to the storage and recall of conscious memories. It can be separated into episodic memory (personal events or experiences) and semantic memory (facts or general knowledge).
In declarative memory tests, subjects are required to recall a list of items (digits, letters, words or pictures) or a complex figure, immediately after the presentation (immediate recall) and after a delay of 20–30 min (delayed recall).

Procedural memory

Procedural memory (implicit memory) refers to the memory system responsible for the encoding, storage and retrieval of procedures and cognitive skills without conscious awareness of these previous experiences. Procedural memory can be assessed with a wide variety of behavioural paradigms including tasks that requires the repetition of a sequence of movements (e.g., finger-tapping) or fine motor control (e.g., to follow a line with a pencil).

Working memory

Working memory refers to the ability to temporarily store and manipulate the information necessary to perform the ongoing task. Working memory can be assessed with a wide variety of behavioural paradigms that require subjects to constantly monitor and update information (e.g., repeat a sequence of moves in the correct order, respond when the presented stimulus matches the one presented in previous trials, repeat alternating sequences of letters and numbers).

Learning

Learning refers to the processing and acquisition of factual information and skills determined by practice or experience. Several methods are used to evaluate verbal learning such as immediate and delayed recall of brief prose passage and multiple-trial list-learning task.

Inhibition

Cognitive inhibition refers to the ability to deliberately or unintentionally suppress or slow-down the processing of stimuli that are irrelevant to the task at hand.
Response inhibition is measured with tasks in which subjects are required to respond only to given stimuli while ignoring distractors; the specific responses that have to be inhibited differ across tasks.

Set-shifting

Set-shifting refers to the ability to rapidly switch between different tasks, mental sets or strategies and thus efficiently adapt to different situations.
Set-shifting is typically investigated using paradigms that required alternating between two or more tasks. Performance on these tasks is typically challenged when a switch from one task to another is required.

Planning

Planning refers to the ability of mapping out a sequence of moves and actions in preparation for the task. This function requires conceptual skills to set goals create and maintain a future-oriented plan to achieve these goals and to select the most appropriate actions based on the anticipation of consequences.

Flexibility

Cognitive flexibility refers to the ability of switching between thinking about two or more concepts simultaneously and reacting accordingly to the changing task demands. The behavioural paradigm used to assess cognitive flexibility requires subjects to track and systematically switch between two or more target stimuli or response modalities.

Reasoning

Logical reasoning refers to the ability of using rational and systematic series of steps in order to draw conclusions, make predictions, or construct explanations.

Reasoning is assessed with tasks that require the subject to analyze different sets of items (e.g., logical statement, patterns, and graphic sequences) and to find the correct answer to complete the series.

Decision-making

Decision making refers to a set of cognitive functions used to evaluate the best choice among a set of alternatives. The decisions-making process can vary depending on the presence of immediate or delayed rewards and their affective value for the decision maker. Several paradigms exist to investigate this function both in the laboratory and in real-life contexts.

Emotional processing

Emotional processing refers to the set of abilities used to recognize, categorized, and understand emotions. This processing is mainly based on the biological and social "value" assigned by an individual to an environmental stimulus. Several paradigms have been developed to measure emotion processing, mainly based on the assessment of the behavioural and physiological responses associated with the vision of emotional stimuli classified in terms of affective valence (positive vs. negative) and arousal (low vs. high).

Creativity

Creativity refers to the personal attitudes and cognitive abilities needed to produce ideas that are considered both potentially original (novel or nonobvious) and effective (valuable or appropriate). Creative thinking involves divergent thinking (generating alternative solutions to an open ended problem) and convergent thinking (integrating elements into a new original synthesis). An example of divergent thinking task is requiring participants to generate many alternative uses for common objects, while an example of convergent thinking task is giving participants three words and asked them what word the previous three words are related to.

Fluency

Fluency refers to the cognitive function that facilitates memory information retrieval. It is a complex cognitive function that involves rule-guided search and retrieval strategies.
Verbal fluency tests required the subjects to generate as many words as possible from different categories within a given time (usually 1 min); it comprises semantic (list all animals, vegetables or professions) and phonetic subtests (i.e., name all the words that begin with a given letter, usually F, A and S).

Results on alertness reaction overall seem to suggest that, in short tasks, NT1 patients can compensate the RTs slowing and display alertness reaction comparable to that of controls. ERP studies elucidated that the slowdown of response speed is not ascribable to a deficit in perception as no abnormalities were observed in early ERP components (N1 and P1) related to stimuli processing. On the other hand, NT1 patients show prolonged latencies and reduced source strength in the later N2 and P3 components that are typically related to stimuli evaluation and attentional engagement, which could reflects a reduction/misallocation of attentional resources to stimuli processing. Similarly, studies that investigated the brain areas involved in sustained attention performance documented widespread hypermetabolism in several brain regions in NT1 patients, which analogously could reflect a compensatory activation related to the increasing cognitive effort.

Sustained attention and vigilance are the attentional functions in which NT1 patients exhibit the most consistent impairments displaying an increase error rate and error rate variability and a quality of performance that markedly declines as a function of time-on-task. Similarly, NT1 patients show impaired simulated driving performance (collisions and off-road driving). Conversely, studies on selective attention show that NT1 patients are able to achieve a performance comparable to that of controls in terms of correctly identified target and search strategies adopted, although they may need more time to complete the tasks.

Studies on divided attention and more complex attentional processes provided less unequivocal results but overall indicate that, apart from slower and more variable RTs, NT1 patients display poor performance in tasks with higher complexity and cognitive load, which suggest a deficit in executive control of attention.

Memory

Memory span

Memory span (the longest list of items that can be correctly repeated immediately after presentation) has been evaluated with

different item lists (words, letter and numbers) and presentation modality (visual, acoustic). In all the studies that assessed the digit span, with the exception of the study by Park, NT1 patients' performance was comparable to that of controls [10,17,18,30,31,33]. Park showed that NT1 patients reported fewer digits compared to controls on forward and backward presentation [34]. Witt assessed the digit and listening span without showing any difference between NT1 and controls [35]. Medrano-Martinez assessed digit and arithmetic spans. NT1 displayed a performance comparable to that of controls on digit reproduction but reported fewer items on the arithmetic test [29]. Total sample assessed: 243 NT1 compared to 15 IH and 266 healthy controls.

Declarative memory

Declarative memory (explicit memory) refers to the memory system dedicated to the storage and recall of conscious memories. Declarative memory has been measured through immediate or delayed recall of items (digits, letters, words or pictures) or of a complex figure. Several studies used the Wechsler memory scale (WMS) without showing differences in memory quotient between NT1 and controls [36–40]. Immediate and delayed visual memory has been assessed with the Rey complex figure and was unimpaired in NT1 [31,35,41] with the exception of Park's study that reported worse performance in NT1 patients than controls [34]. Naumann assessed verbal memory, through immediate and delayed recall of a prose passage and of three structured word lists, reporting that NT1 patients recalled fewer items from both tasks than controls [10]. In the same study Naumann assessed visual memory (Benton visual retention test) reporting no difference between NT1 patients and controls. Finally, Saletu administered the Grünberger's verbal memory test and did not find differences between NT1 and controls [16]. Total sample assessed: 225 NT1 compared to 230 healthy controls.

Procedural memory

Procedural memory (implicit memory) refers to the memory system dedicated to the encoding, storage, and retrieval of motor, visuospatial, or cognitive skills. Procedural memory has been investigated by quantifying changes in speed and accuracy across testing sessions.

Cipolli assessed procedural learning of visual discrimination skills administering the texture discrimination task in a study comprising three experimental sessions (training, 1st-d and 7th-d retrieval) [38]. NT1 displayed impaired procedural learning presenting lower accuracy on the training session and less effective consolidation of visual skills compared to controls on training, 1st-d and 7th-d retrieval. Using a similar research design, Mazzetti explored procedural learning of motor skills through the finger-tapping test [40]. The authors found no difference in performance accuracy, but NT1 patients displayed slower performance speed compared to controls. The consolidation process emerged as less effective in NT1 patients, who displayed lower improvement across sessions than controls. Finally, Mazzetti assessed how the activation of semantic memory differs in REM sleep compared to wakefulness using the semantic priming paradigm [36]. NT1 and control completed a lexical decision task (deciding whether the word presented is a real word or a pseudoword) twice in wakefulness and twice after awakening from REM-sleep. The authors reported no difference in accuracy; however, NT1 displayed reduced semantic priming effect (longer RTs) than in controls. Total sample assessed: 43 NT1 compared to 43 healthy controls.

Working memory

Working memory, the memory system dedicated to temporal storage and manipulation of information, has been assessed with tasks that require online information monitoring and updating. Performance is reflected by errors, correctly remembered sequences, and the longest remembered sequence. Several studies used the Corsi block-tapping test (CBTT). Yoon and Park showed that NT1 remembered fewer sequences than controls for both forward and backward conditions [30,34]. By contrast, Kim and Ha found no differences in CBTT forward and backward scores and in the longest remembered sequence [14,31]. Ha further assessed working memory through the work performance series test reporting lower working memory capability in NT1 compared to controls. Two studies used the 2-back test. Naumann showed that NT1 display slower RTs than controls but comparable quality of performance [10]. Bayard reported slower RTs and increased error rate in NT1 compared to controls while no difference emerged with NT2 patients [13]. Moraes administered the letter-number sequencing test and reported fewer recalled items in NT1 than controls [32]. Witt investigated changes in brain activity (functional magnetic resonance imaging, fMRI) during a verbal working memory task [35]. NT1 patients displayed a quality of performance comparable to that of controls but presented increased deactivation within the default mode network. Total sample assessed: 185 NT1 to 22 NT2 and 198 healthy controls.

Learning

The ability to learn new verbal material has been investigated through verbal learning tasks. Performance is reflected by immediate recall, short and long delay free and cued recall. In all studies that used the California verbal learning test (CVLT), with the exception of Park's study, no differences emerged between NT1 and controls [30,31,41]. Park reported reduced ability to learn new verbal material, an impaired immediate and delayed free recall in NT1 than controls [34]. Two studies used the auditory verbal learning test and in both no differences emerged between NT1 and controls in terms of learning capacity, immediate/delayed free recall and recognition [12,17]. Total sample assessed: 184 NT1 compared to 15 NT2 and 168 healthy controls.

Summary

Evidence of memory deficits in NT1 patients is scarce and limited to specific memory functions. Memory span has been extensively evaluated and, with the exception of a single study, no evidence of impaired performance has emerged. Similar conclusions can be drawn regarding memory quotient and visual-spatial memory, which did not prove to be impaired in all but one study. Verbal memory and learning performance are unimpaired in NT1 patients. Conversely subtle alteration have emerged in procedural memory as NT1s display slower procedural learning and less effective memory consolidation. Working memory is impaired in NT1 patients who remember fewer sequences, make more errors and display slower and more variable RTs. Noteworthy, the only study that investigated brain activity changes during a working memory task showed that NT1 patients do not present altered activity over frontal areas, associated with working memory performance, but increased deactivation of the default mode network, which is usually observed in response to greater task-related effort.

Executive functions

Inhibition

Cognitive inhibition refers to the ability to suppress the processing of stimuli that are irrelevant for the task at hand, measured as the number of commission errors and the RTs difference between congruent and incongruent trials (i.e., interference effect). Three studies used the Go-NoGo test. Delazer reported no difference in commission errors between NT1 and controls; however,

fewer patients performed at ceiling than controls (61% vs 81%) in the Go-trials and a higher percentage of NT1 (85%) obtained a score below the cut-off in the NoGo-trials [18]. Zamarian reported lower accuracy in NT1 compared to controls in the Go-trails and no difference in the NoGo-trials. Similarly to the study of Delazer, a lower percentage of patients displayed performance at ceiling in the Go-trials than controls (65% vs 89%) [17]. Bayard administered the Go-NoGo to NT1, NT2 patients and controls and did not find differences in performance accuracy but reported slower and more variable RTs in NT1 compared to NT2 patients and controls [13]. Several studies adopted the Stroop test and its variants. Park and Yoon administered the Stroop and reported no differences between NT1 and controls in terms of correct responses and RTs to correct responses [30,34]. Similarly, Kim and Medrano-Martinez did not find any differences between NT1 and controls at the Stroop word and colour test [29,31]. Moraes administered the Victoria Stroop without showing differences in accuracy between NT1 and controls but patients displayed slower RTs than controls [32]. Van Holst investigated the brain activity changes associated with two kinds of response conflicts by administering the Stroop and the Food Stroop (target stimuli are replaced with food-related words and neutral-words) to NT1, IH patients and controls in an fMRI protocol [33]. No differences were observed in terms of error rate and interference index but NT1 patients showed increased activity to food-words (compared to neutral-words) in the ventromedial prefrontal cortex and reduced activation to incongruent-words (compared to congruent-words) in the dorsomedial prefrontal cortex. Finally, Naumann administered the Hayling sentence completion test (complete sentences using connected and unconnected words) and reported increased error rate and slower RTs for response initiation and inhibition in NT1 than in controls [10]. Total sample assessed: 273 NT1 compared to 22 NT2, 15 IH and 301 healthy controls.

Set-shifting

The ability to adaptively shift attention and action has been investigated with the Trail Making test (TMT), the intra/extra dimensional set-shift test, and the Wisconsin card sorting test (WCST). The TMT comprises two parts TMT-A (visual control and processing speed) and TMT-B (attentional shifting), the difference in time to complete the two parts reflects the cognitive cost of attentional shift.

With the exception of the studies of Park and Moraes, no differences emerged between NT1 and controls in the time needed to complete both parts of the TMT [29–31,36–40]. Park and Moraes showed that NT1 patients need more time than controls to complete both parts of the TMT [32,34]. The latter also reported a greater time cost of attentional shift in NT1 compared to controls, while this difference was not observed in the study of Medrano-Martinez [29]. Delazer and Zamarian administered the intra/extra dimensional set-shift test and did not find differences between NT1 and controls in the number of completed stages, trials needed to complete a stage, errors and errors adjusted for number of stages [17,18]. Two studies used the WCST. Yoon did not find differences between NT1 and controls [30]. Huang investigated the relationship between WCST and brain activity (PET) in NT1, NT2 and controls [26]. NT1 patients displayed lower perseverative response and error T scores than controls while no difference emerged compared to NT2 patients. In NT1 patients, hypometabolism over frontal and parietal lobe correlated with perseverative responses and errors on the WCST. Total sample assessed: 407 NT1 compared to 29 NT2 and 355 healthy controls.

Planning

The ability to map out a sequence of moves is measured as the number of problems solved, the number of moves needed to complete the problem, and the time required to complete the test. Delazer administered the one touch stockings of Cambridge test and did not find differences between NT1 and controls [18]. Similarly Zamarian administered the same test and did not find differences in the number of problems solved on the first choice and in the mean latency to the correct choice between NT1 and controls [17]. Medrano-Martinez administered the zoo map test and did not find differences between NT1 and controls [29]. Total sample assessed: 100 NT1 compared to 121 healthy controls.

Flexibility

The ability to shift attention between different tasks, responses, concepts or strategies has been measured in terms of error rate and errors/RTs decrement in switch conditions.

Naumann administered the incompatibility test showing that NT1 were slower than controls without differing for performance accuracy [10]. Similar results have been reported by Ha who administered the Cognitrone test and did not find differences between NT1 and controls in performance accuracy, but reported slower RTs in NT1 [14]. Ha also administered the determination unit test (accuracy and response speed to visual and acoustic stimuli presented at three different speeds) and reported worse performance accuracy in NT1 than in controls for all presentation speeds, although the difference becomes more salient with the fastest stimuli. Bayard administered the flexibility task to NT1, NT2 patients and controls reporting increased errors in NT1 patients than controls while no difference emerged with NT2 patients [13]. Rieger administered the alternation reaction test and showed that NT1 made more errors and had slower and more variable RTs than controls [12]. Total sample assessed: 80 NT1 compared to 22 NT2 and 89 healthy controls.

Reasoning

The ability to use rational and systematic series of steps to draw conclusions or make predictions has been measured with the Baddeley logical reasoning test [36–40], the Raven's progressive matrices and the Hypothesis formation test [14,30]. Relevant measures are the number of series completed and the composite reasoning score. No differences emerged between NT1 and controls in any of the studies. Total sample assessed: 136 NT1 compared to 136 healthy controls.

Summary

Overall, NT1 patients display high performance in several neuropsychological domains involving executive functioning. Regarding response inhibition, despite the overall slowing of processing speed, NT1 patients generally display intact quality of performance.

Differences between NT1 patients and controls in response inhibition are indeed slight (i.e., a lower percentage of patients who perform at ceiling) or limited to specific tasks.

However, a recent study that investigated the neurocognitive mechanisms underlying response conflicts showed that, despite an intact quality of performance, NT1 patients display increased activity in brain areas related to executive functions and attention control during the classic Stroop and increased activity in fronto-striatal regions, associated with the reward behaviour, in response to food-related words. Logical reasoning and spatial planning were unimpaired in all studies examined. Overall, set-shifting ability is not impaired in NT1 patients, which show a quality of performance comparable to that of controls although they may need more time to complete the task. Again, neuroimaging studies (PET) did not document altered activity over brain areas associated with set-shifting [42] in NT1 patients who show marked hypermetabolism in several brain regions while

performing the tasks. Finally, NT1 patients display an impaired cognitive flexibility presenting slower RTs and more errors than controls in the majority of studies.

High order cognitive functions

Decision-making

Decision-making refers to a set of functions dedicated to evaluating the best choice among a set of alternatives depending on the presence of rewards and their affective value. Bayard used the Iowa gambling task (IGT) to assess implicit learning and the Game of dice task (GDT) to assess decision-making under risk [43]. NT1 displayed a worse IGT performance, with a higher percentage of patients who achieved a net score <0 (money gained or advantageous minus disadvantageous card selection) compared to controls (57% vs 13%). Moreover, among patients who achieved a net score <0 the majority displayed lack of perseverance. Differences between NT1 and controls become more salient in the last blocks when controls made a higher number of advantageous choices compared to NT1 patients.

No difference emerged between NT1 and controls on the GDT in terms of net scores and difference between risky and non-risky choices. In a subsequent study, Bayard confirmed the impaired performance on the IGT in NT1 patients compared to controls but did not find differences in perseverance [44]. Bayard also assessed the effects of pharmacological treatment on decision-making and did not find differences in IGT and GDT measures between drug-naïve NT1 and patients treated with stimulants.

Delazer showed that controls increased the advantageous choices across IGT blocks while NT1 made more disadvantageous choices and shifts between decks in the last blocks [18]. Moreover, a lower percentage of NT1 patients displayed a significant strategy index (ability to adapt strategy when a choice leads to a negative outcome) compared to controls (14% vs 40%). Delazer also assessed reward sensitivity and impulsivity through the information sampling task (IST). NT1 patients made decisions with a higher degree of uncertainty and did not adapt their response pattern, displaying a lower probability of being correct at the point of decision than controls [18]. Finally, Dimitrova administered the balloon analogue risk task to NT1, NT2 patients and controls and did not find group differences in any of test measures [24]. Total sample assessed: 115 NT1 compared to 15 NT2 and 153 healthy controls.

Emotional processing

Emotional processing refers to the set of abilities dedicated to recognizing, categorizing, and understanding emotions. Overall, studies in this field explored the behavioural and neurophysiological reactions of NT1 patients to a set of emotional stimuli varying in terms of valence and arousal. Tucci analyzed ERP components, electromyography, electrocardiogram, and skin conductance in response to positive, negative, and neutral stimuli [45]. NT1 patients displayed lower cardiovascular (smaller pressure decrease and lower heart rate) and electrodermal reactivity, and milder autonomic and muscular reactivity (mylohyoid) in response to unpleasant stimuli than controls. ERP analysis showed reduced amplitudes in N2 and P3 components during the vision of unpleasant stimuli in NT1. Khatami assessed the modulation of the acoustic startle reflex, which is typically enhanced during unpleasant stimuli processing and decreased during the pleasant stimuli processing. Unlike controls, NT1 did not exhibit the amygdala-dependent startle potentiation during the presentation of unpleasant images [46]. De Zambotti explored the behavioural (ratings of arousal and valence) and hemodynamic responses to emotional stimuli as well as the coping strategies adopted by NT1 patients [47]. No difference emerged between NT1 and controls in the hemodynamic response but patients evaluated emotional stimuli as less arousing and pleasant. Concerning coping strategies, NT1 were less focused and showed reduced expression of their emotions. Schwarz assessed the neural correlates of emotional processing through fMRI [48]. NT1 patients displayed reduced activity in the hypothalamus and medial frontal cortex (anterior cingulate, left anterior insula and orbitofrontal) and increased activity in the right amygdala, right inferior parietal and fusiform cortex during the vision of humorous pictures. Reiss examined the neural correlates of emotional processing by showing NT1 patients humorous cartoon. NT1 rated fewer cartoons as funny compared to controls and displayed increased activity in the nucleus accumbens and hypothalamus [49]. Ponz evaluated the neural correlates of affective response to reward administering the monetary incentive delay task [50]. No differences emerged in behavioural performance (failed trials and hits) between NT1 and controls, however, patients displayed lack of activation in the ventromedial prefrontal cortex and nucleus accumbens, during high-incentive trials, and enhanced activity in the dorsal striatum coupled with lack of response in ventral striatum during winning trials. In a subsequent study Ponz investigated the neural correlate of anticipation of reward by administering a triangle-orientation task coupled with painful electrical stimulation as aversive conditioning [51]. No difference emerged in accuracy and RTs between NT1 and controls, however, patients did not show changes in amygdala activity or in the functional coupling between the amygdala and the medial prefrontal cortex in response to the conditioned stimulus. Total sample assessed: 73 NT1 compared to 75 healthy controls.

Creativity

Creativity refers to the set of abilities required to produce potentially original and effective ideas. Lacaux assessed divergent-exploratory thinking (the ability to generate many possible solutions based on a given stimulus) and convergent-integrative thinking (the ability to integrate in an original way a set of elements) administering the evaluation of potential creativity test to NT1, NT2 and controls [52]. NT1 displayed higher scores for originality and elaboration in the convergent task and a tendency to score higher in the divergent task than controls. Total sample assessed: 131 NT1 compared to 54 NT2 and 126 healthy controls.

Fluency

Fluency refers to the set of cognitive functions that facilitates memory retrieval and is measured as the total number of items produced for a specific category (semantic, phonemic) within the allotted time. Yoon assessed verbal fluency with the controlled oral word association test (COWAT) and the Boston naming test and did not find differences between NT1 and controls [30]. Similarly, Kim and Delazer did not find differences between NT1 and controls in any of the COWAT measures [18,31]. Medrano-Martinez administered the COWAT and reported worse phonemic fluency in NT1 than in controls [29]. Conversely, Park administered the COWAT and reported reduced semantic fluency in NT1 compared to controls [35]. Finally, Zamarian and Naumann showed that NT1 patients generated fewer words in the semantic and phonemic conditions compared to controls [10,17]. Total sample assessed: 209 NT1 compared to 232 healthy controls.

Intelligence

Intelligence quotient (IQ) has been assessed in five studies with the revised version of the Wechsler adult intelligence scale [36–40]. No difference emerged between NT1 patients and controls in total IQ, verbal IQ and performance IQ. Total sample assessed: 79 NT1 compared to 79 healthy controls.

Summary

Studies on higher-order cognitive processes have documented a number of impairments in NT1 that cannot be solely explained by the difficulties emerging in more "basic" cognitive functions. In the area of decision-making, the agreement among several studies is that NT1 patients display poor performance in decision-making under ambiguity but unimpaired performance in decision-making under risk. When performing a decision-making task where outcome probabilities are not completely known and cannot be completely anticipated, NT1 are less flexible in adapting their responses after a negative feedback, displaying a higher tolerance to uncertainty, and tend to opt more frequently for choices with high immediate reward but leading to negative consequences in the long run. Although studies on the neural correlates of decision-making in NT1 are lacking, several authors suggested that this impaired profile might result from abnormal activity in brain regions essential for the processing of uncertainty and rewards. Regarding emotional processing, NT1 patients display several abnormalities in the neurophysiological responses to unpleasant stimuli, namely absence of the amygdala-dependent startle potentiation reflex, reduced cardiovascular, electrodermal, autonomic and muscular reactivity and reduced amplitude of the N2 and P3. Brain imaging studies extended these findings documenting altered activity in the amygdala and hypothalamus in response to both pleasant and unpleasant stimuli. Studies of verbal fluency provided conflicting results. NT1 patients showed reduced verbal fluency in half of the studies but no discrepancies emerged between semantic and phonemic fluency. Finally, a notable exception among is represented by creativity that is increased in NT1 patients.

Narcolepsy Type 2

Six studies investigated cognitive functions in NT2 patients, all assessing multiple cognitive domains in parallel (see Box 1).

Attention

Phasic and tonic alertness has been assessed in the studies of Bayard and Filardi.

Bayard administered a simple and forewarned RTs task and did not find differences between NT2 and controls in terms of RTs and RTs variability [13]. Filardi administered the ANT and showed slower RTs in NT2 compared to controls while no difference emerged in the alerting, orienting and executive control network [28]. Dimitrova assessed **sustained attention and vigilance** in NT2, NT1 patients and controls through the PVT and reported slower RTs in NT2 patients than controls [24]. Van Schie administered the SART to NT2, NT1, IH and OSAS patients and did not find group differences in any of the task measures [22]. Huang assessed vigilance in NT2 patients compared to NT1 and controls administering the CPT in a PET study protocol. NT2 displayed slower and more variable RTs, a higher CPT clinical confidence index (performance closer to a clinical profile) and a higher RT block change T score (trend towards slower responses across task blocks) compared to controls [26]. NT2 presented hypermetabolism in several brain regions and hypometabolism in the Heschl's gyrus and paracentral lobule compared to controls. Total sample assessed: 86 NT2 compared to 219 NT1, 37 IH, 12 OSAS and 108 healthy controls.

Memory

Bayard assessed **working memory** administering the 2-back to NT2, NT1 patients and controls [13]. NT2 displayed an increased error rate compared to controls while no differences emerged in RTs and RTs variability. Total sample assessed: 22 NT2 compared to 22 NT1 and 30 healthy controls.

Executive functions

Bayard assessed **inhibition** and cognitive **flexibility** administering the Go-NoGo and the flexibility test. No differences emerged on the Go-NoGo in terms of errors but NT2 displayed slower RTs than controls. Conversely, NT2 patients made more errors and displayed more variable RTs on the flexibility test compared to controls [13]. Huang assessed **set-shifting** administering the WCST and found impaired performance in NT2 relative to controls in terms of perseverative response and errors [26]. Total sample assessed: 51 NT2 compared to 126 NT1 and 56 healthy controls.

Higher order cognitive functions

Dimitrova assessed **decision-making** administering the balloon analogue risk task to NT2, NT1 patients and controls without showing difference in any of test measures [24]. Lacaux assessed **creativity** administering the evaluation of potential creativity test and showed increased creativity in NT2 patients compared to controls [52]. Total sample assessed: 69 NT2 compared to 161 NT1 and to 156 healthy controls.

Summary — Narcolepsy Type 2

The most consistent impairments in NT2 patients were observed in the attentional area. Tonic and phasic alertness have been assessed in only two studies with conflicting results, while sustained attention and vigilance emerged as consistently impaired in NT2 patients who make more errors, present slower RTs and a decline in RTs over time-on-task. Overall, the attentional profile shown by NT2 patients seems to partially overlap the NT1 profile, although direct comparison between the two disorders reveals that attentional impairments are more severe in NT1. Working memory has been assessed only in one study and proven impaired in NT2 compared to controls. Concerning executive functions, response inhibition was not impaired even if NT2 patients exhibited slower RTs. NT2 displayed impaired performance in cognitive flexibility and set-shifting compared to controls. In the area of higher order cognition results are limited to decision-making and creativity that, although being investigated only in single studies, are not impaired in NT2.

Idiopathic Hypersomnia

Only four studies assessed cognitive functions in IH patients. Attention, memory and executive functions have been investigated; no study assessed higher order cognition (see Box 1).

Attention

Raam assessed attention in two separate studies. In the first study they assessed **alertness, selective attention, divided attention, sustained attention and vigilance** in IH, NT1, subjective EDS and controls [7]. IH displayed impaired performance on the alertness task (slower RTs for both phasic and tonic alertness) and on the vigilance task with patients displaying impaired performance and a progressive increase of RTs and errors over time-on-task. Beyond slower RTs, IH patients showed a performance comparable to that of controls on the selective, sustained and divided attention tasks. In the second study Raam assessed **selective attention** and **vigilance** [19]. IH displayed slower RTs on the selective attention and on the vigilance task, but intact quality of

performance compared to controls. The authors confirmed the decline of performance over time-on-task in IH that, unlike subjective EDS and controls, presented increased omission errors in the second part of the task compared to the first one. Van Schie assessed vigilance (SART) in IH, NT1, NT2 and OSAS patients and did not find group differences in any of the SART measures [22]. Total sample assessed: 65 IH compared to 61 NT1, 5 NT2, 13 subjective EDS, 12 OSAS and 40 healthy controls.

Memory

Van Holst administered the digit span test without showing differences between IH patients and controls [33]. Total sample assessed: 15 IH compared to 23 NT1 and 20 healthy controls.

Executive functions

Van Holst investigated the brain activity associated with response conflicts administering the Stroop and the food Stroop to IH, NT1 patients and controls during fMRI scan [33]. IH patients presented increased activity in the ventromedial prefrontal cortex on the Stroop test compared to controls. Total sample assessed: 15 IH compared to 23 NT1 and 20 healthy controls.

Summary — Idiopathic Hypersomnia

A realistic overview of the cognitive profile of IH patients can be formulated only for attention since memory and executive functions have been poorly investigated and high order cognition have not been investigated at all. Regarding attention, IH patients show slower RTs and an increase in RT variability over time-on-task on vigilance tasks, but a performance comparable to that of controls on selective, sustained and divided attention. The only study that assessed memory showed that IH patient's memory span is comparable to that of controls. Similarly, only one study assessed executive functions, namely response inhibition, and showed that IH patients display a performance comparable to that of controls, but display reduced activity in the middle cingulate cortex during the Stroop test.

Kleine-Levin syndrome

Five studies assessed cognitive function in KLS (see Box 1). All studies assessed patients with active disease who were evaluated between hypersomnolence episodes.

Attention

Landtblom assessed **alertness**, by means of simple RTs, and **selective attention**, through the Ruff 2—7 test, in four KLS adolescents and reported intact performance in all but one KLS patients (which presents a slight mental retardation) [53].

Memory

Landtblom assessed **memory span** with the digit span test and reported a reduction of memory capacity in KLS patients compared to normative data [53]. Similarly, in the study of Uguccioni KLS patients reported fewer digits on the forward digit span compared to controls [54]. Engstrom administered the digit span and the listening span test [55]. KLS patients displayed a performance comparable to that of controls on the digit span but reported fewer items on the listening span. Landtblom and Uguccioni assessed visuospatial **memory** through the Rey complex figure and reported unimpaired performance in KLS patients [53,54]. Lambton also administered the Benton visual retention test and reported impaired performance in KLS patients compared to normative data. Uguccioni assessed verbal memory (free and cued selective reminding test) and reported impaired recovery immediate and delayed free recall in KLS patients than controls [54].

Working memory and its neural correlates (fMRI) have been investigated in three studies. Engstrom administered a working memory task and the digit span prior and during fMRI scanning. KLS patients recalled fewer words compared to controls outside the scanner and displayed lower accuracy and slower RTs during the fMRI session. In KLS patients working memory performance correlated with reduced activity in anterior cingulate and dorsomedial prefrontal cortex and increased activity in medial and anterior thalamus [55]. In a subsequent study Engstrom analyzed brain activity in the salience network (anterior insula and anterior cingulate cortex). Patients were split into high- and low-capacity [56]. KLS patients displayed lower accuracy, slower RTs and increased activity in the salience and executive network than controls, although with a different pattern of activity between high- and low-capacity patients. Finally, Engstrom assessed thalamic response during a working memory task [57]. KLS patients displayed poor performance compared to controls and increased thalamic activity, while controls showed decreased thalamic activity during the task. Again, the pattern of brain activity differs between high- and low-capacity patients (higher thalamic response in high-capacity patients). **Procedural memory** and verbal **learning** had been evaluated in the study of Landtblom through finger-tapping and the auditory verbal learning test; in both tasks KLS displayed unimpaired quality performance compared to normative data [53]. Total sample assessed: 170 KLS compared to 106 healthy controls.

Executive functions

Response **inhibition** has been assessed with the Stroop and the Stroop color word test. Landtblom administered the Stroop and reported unimpaired performance in all but one KLS patient [53]. Uguccioni administered the Stroop color word and reported more colour error, colour-word error, interference errors and slower RTs in KLS patients than controls [54]. **Set-shifting** has been assessed with the TMT and the WCST. Landtblom reported unimpaired performance on both tests in KLS patients [55]. Uguccioni did not find differences on the TMT-A, but showed that KLS patients need more time to complete the TMT-B than controls [54]. Cognitive **flexibility** has been assessed in the study of Landtblom with the paced auditory serial addition test and did not prove impaired in KLS patients [53]. Total sample assessed: 126 KLS compared to 42 healthy controls.

Higher order cognitive functions

Landtblom assessed verbal **fluency** through the COWAT and reported unimpaired performance in KLS patients [53]. Uguccioni assessed semantic and phonemic fluency and did not find differences between KLS and controls [54]. **Intelligence** has been assessed in two studies. Landtblom reported normal IQ in three KLS patients and slight mental retardation in one patient [53]. Uguccioni reported a lower non-verbal IQ in KLS patients compared to controls [54]. Total sample assessed: 126 KLS compared to 42 healthy controls.

Summary — Kleine-Levin syndrome

KLS patients display reduced memory capacity (digit and listening span) and declarative memory, while visuospatial memory, procedural memory and verbal learning were unimpaired. Working memory also emerged as compromised in KLS patients

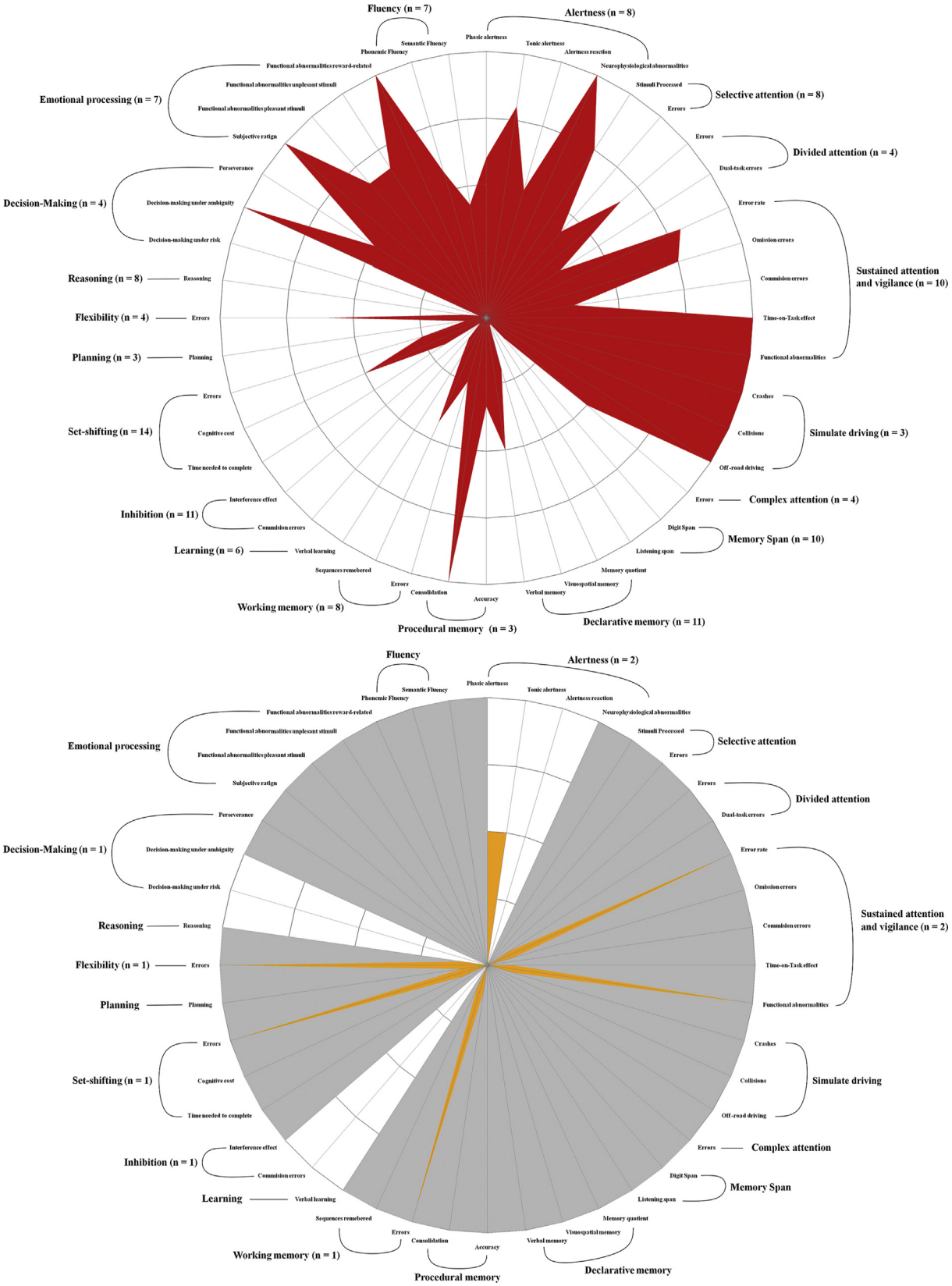
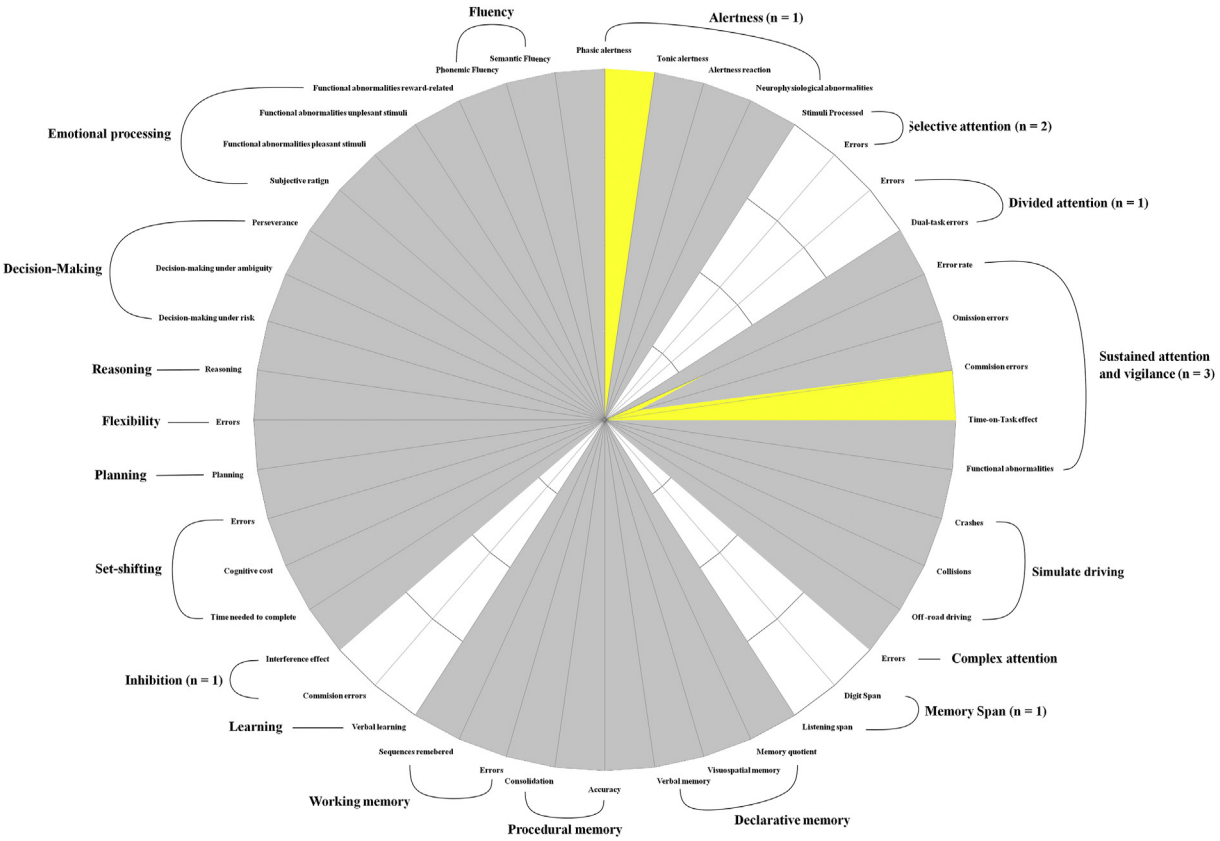


Fig. 2. Profile plots of CDH patients. Data plotted are the number of studies that found reduced performance in CDH patients relative to healthy controls, standardized to the total number of studies available for the cognitive domain analyzed. Axes values ranges from 0 (i.e., the blank areas, which indicates that no studies found reduced performance) to 100 so that higher values uniformly indicate reduced performance. The cognitive functions for which no studies are available are colored in gray. Red = cognitive profile of NT1 patients; orange = cognitive profile of NT2 patients; yellow = cognitive profile of IH patients; green = cognitive profile of KLS patients.



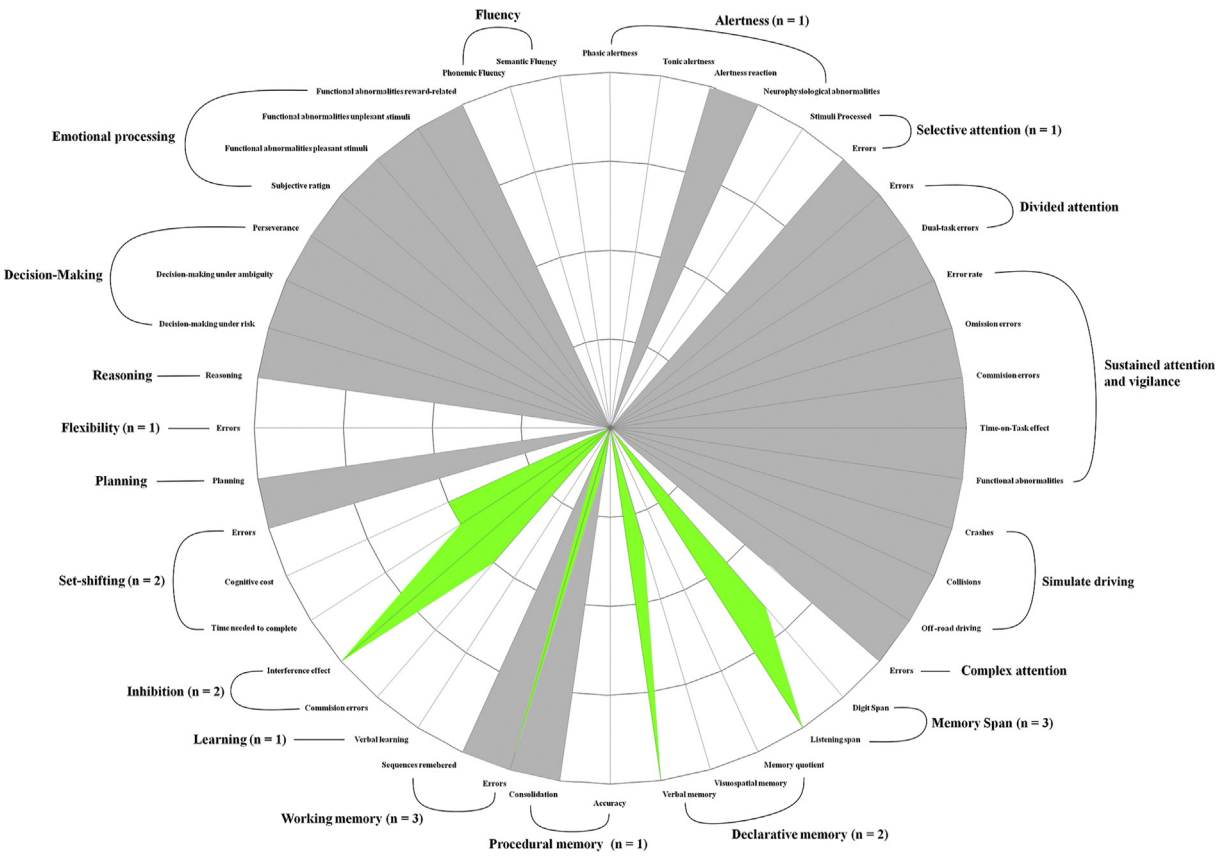


Fig. 2. (*continued*).

who make more errors, recall fewer words, and exhibit slower RTs. Moreover, KLS patients present increased reactivity in the thalamus, inferior left frontal cortex, dorsolateral prefrontal cortex and a reduced activity in the medial frontal cortex and anterior cingulate during a working memory task, although the functional implications of this abnormal activity pattern have yet to be clarified. Attention has been studies only in one study with a small sample and proven unimpaired in KLS patients. Concerning executive functions and higher-order cognition, KLS patients display a performance comparable to that of controls in tasks assessing inhibition, set-shifting, flexibility and verbal fluency but exhibit lower non-verbal IQ scores than controls.

Discussion

In this review we summarized all the studies that have assessed cognitive impairments among CDH patients. Over the last two decades (2000–2020) studies on cognitive functioning in CDH have been overall rather sparse and markedly skewed in favour of NT1.

The marked imbalance between studies stems from the discovery that NT1 is caused by the selective loss of hypocretinergic neurons, which sparked a number of studies aimed at elucidate the role of hypocretin deficiency in a wide range of cognitive processes.

As respect to the amount of studies available in the time period 1980–2000 (see the review by Fulda and Schulz for a detailed description) during the last two decades studies on narcolepsy almost tripled (15 vs 44) while unfortunately this is not the case with the other CDHs [58]. Indeed, research on cognitive functioning in these disorders is still in its infancy and several cognitive domains have not been investigated at all in NT2, IH and KLS patients.

As a consequence, the possibility to compare the performance of CDH patients within each cognitive domain is limited to the area of attention and, to a lesser extent, to memory. Consistent evidence points to attentional deficits in NT1, NT2 and IH, conversely, KLS does not appear to be associated with attention impairments, although attentional functions have been far less studied in this disorder (a single study based on four patients).

Impairment at the temporal level of attention processing seems to represent a common feature among NT1, NT2 and IH patients which display slower and more variable RTs in short tasks assessing alertness and impaired performance with a rapid decline of RTs and increase in errors across time-on-task in long and monotonous tasks. Studies directly comparing the performance of these patients showed that NT1 display the most pronounced impairments presenting slower RTs compared to NT2 patients [26,28] and an increased error rate in vigilance tasks compared to IH patients [7,19]. Beside the overall RTs slowing and the decrease of performance over time-on-task, NT1 patients also exhibit poor performance in tasks assessing divided, flexible and complex attention, which indicates impairment in executive control of attention. Clarifying whether this executive attention dysfunction is specific of NT1 is of crucial interest; however, the number of studies is too limited to draw any meaningful conclusion. Indeed the executive control of attention has been poorly studied in the other CDHs and the available evidences is limited to divided attention, which has proved unimpaired in IH and KLS patients, and to flexibility of attention, which proved impaired in both NT2 and NT1 patients instead.

Despite the common complains of memory deficit and forgetfulness CDH patients overall show less pronounced deficits in the area of memory [59].

Memory performance of NT1 is comparable to that of controls for most memory functions: memory span, declarative memory, visuospatial memory and verbal learning. Slight alteration seems to emerge only in the area of procedural memory. Conversely, KLS patients show reduced memory capacity (digit and listening span) and impaired verbal memory. Only one study assessed memory (digit span) in IH patients and reported unimpaired performance. Working memory has been studied in NT1, NT2 and KLS patients, all of which showed impaired performance with slower RTs and increased error rates compared to controls. Noteworthy, studies that investigated the neurocognitive mechanism of working memory performance showed that, within a context of impaired behavioural performance, KLS patients display reduced activity in dorsomedial prefrontal cortex, cingulate and thalamus, while NT1 patients do not show altered brain activity over frontal regions typically associated with working memory but increased deactivation within the default mode network, which is usually observed in response to the task-related mental effort [60].

Scientific literature is more scattered in the broad area of executive functions.

Inhibition is the only executive function investigated across all CDHs and, despite an overall slowing of response speed, it has not proven impaired in NT1, NT2 and IH patients while KLS patients show impaired performance in terms of errors and RTs slowing, although this represents single-study evidence. The set-shifting ability has been investigated in NT1, NT2 and KLS and it does not result impaired in NT1 and KLS patients, while NT2 patients display impaired performance in terms of perseverative responses and errors. Planning and reasoning skills have been investigated only in NT1 and both were unimpaired.

High-order cognitive functions have been studied exclusively in NT1, except for creativity that has been investigated also in NT2.

NT1 patients display a complex pattern of impairment in higher-order cognition that cannot solely result from impairments in attention and executive functions. NT1 patients display poor performance in decision-making under ambiguity presenting a decision pattern characterized by a high tolerance to uncertainty, problems with implicit learning and reduced flexibility in adapting decisions after a negative feedback. Similar alteration has been observed in neurological disorders characterized by a progressive loss of dopaminergic neurons [61]. Hypocretin and dopamine are anatomically and functionally linked, both playing a major role in reward seeking and motivated behaviour [62,63] as recent evidence from animal studies indicates a direct action of hypocretin in regulating dopaminergic activity in the ventral tegmental area [64]. Overall, these findings suggest that this poor decision-making profile might result from altered activity in the reward circuits (basal ganglia, amygdala, hippocampus, thalamus, dopaminergic ventral tegmental area and the limbic–orbitofrontal–striatal loop) [18]. Noteworthy, similar evidence pointing to an impairment of the subcortical pathways related to emotional/motivational engagement emerges from neurophysiological/neuroimaging studies on emotional processing. An altered amygdalar and hypothalamic response to emotional arousing pictures and cartoons has been consistently shown in NT1. Finally, creativity seems to represent a remarkable exception among cognitive functions, as it is increased in both NT1 and NT2 patients and appears to be related to specific narcolepsy's symptoms such as hypnagogic hallucinations and lucid dreaming [52,65]. Graphical representations of studies results are reported in Figs. 2a,b,c,d.

Aside from the comparison between cognitive profiles, our review points out a number of methodological issues that should be taken into account for future research.

First, the studies reviewed employed a number of widely different neuropsychological tasks (67 tasks in 47 studies), which significantly affects the comparability across studies.

A general trend in CDH research is indeed to select specific tasks from neuropsychological assessment batteries (see Table 2), which reduces the replicability of findings and the comparison between single studies results. To overcome this issue, more recent studies [13,28,29] adopted cognitive tests based on validated neurocognitive models of attention and executive functions [66,67], an approach that, beside improving studies comparability, will allow us to understand specific performance impairments within a theoretical framework.

Second, the vast majority of studies reviewed adopted a research design in which multiple cognitive functions were assessed within a single testing session. As a result, the current knowledge on diurnal fluctuation in cognitive performance of CHDs is particularly scarce [20,21], and further studies with a circadian or time-of-day design are especially needed.

Third, as stated above the scientific literature is markedly skewed in favor of NT1: future research should be specifically designed to assess the cognitive impairments experienced by NT2, IH and KLS patients.

The assessment and monitoring of the cognitive impairments experienced by CHD patients has important clinical implications and potentially paves the way to personalized interventions. Indeed, the current pharmacological treatments for CDHs are suboptimal to manage the different cognitive, emotional and behavioral problems experienced by patients. Treatment with modafinil and sodium oxybate improves attentional performance [23,68] but display no effects on emotional processing and decision-making on which behavioural interventions could prove beneficial [44]. As an example, recent studies showed that behavioural training can enhance decision-making ability in healthy subjects and similarly could prove beneficial in NT1 patients [69]. Conversely, behavioural training aimed at improving memory, particularly working memory, could be useful in KLS patients who display both impaired performance and reduced brain activity in working-memory associated areas.

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Practice points

1. Attention impairments are common among NT1, NT2 and IH patients which show slower RTs and a significant decline of performance across time-on-task. NT1 patients display the most compromised profile and impaired quality of performance in tasks with higher cognitive load.
2. Performance of KLS patients at memory test is severely compromised in terms of errors, number of recalled items and RTs slowing, whereas it is not impaired in NT1 and NT2. KLS patients should be supported with specific memory training.
3. Scant evidence is present for executive functions, overall preserved in NT1, except for flexibility which resulted impaired in both NT1 and NT2 patients.
4. Evidence on higher-order cognitive functions is mainly traceable in NT1 patients, who display poor decision-making skills and impaired emotional processing. Creativity seems increased in both NT1 and NT2.

Research agenda

1. Most studies focused on NT1, probably due to the well-known underlying neurobiological system, while studies on cognitive functions in NT2 and IH patients are extremely rare.
2. Future studies on higher-order cognitive functions in NT1 and NT2 patients are warranted. A deeper characterization of the high-level cognitive functioning could pave the way to personalized interventions and improve patients' quality of life.
3. Novel investigations on neural correlates of cognitive functioning in CDH patients are necessary, as they have been scarcely investigated, except for the studies of emotional processing in NT1.

Conflicts of interest

Giuseppe Plazzi participated in advisory board for UCB Pharma, Jazz pharmaceuticals, Bioprojet and Idorsia, outside the submitted work. The other authors have no potential financial conflict of interest/competing interest to disclose.

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