Decision-making in people with narcolepsy and healthy age-matched controls

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Our objective is to investigate decision-making in people with narcolepsy with and without cataplexy and compare it to that of age-and sex-matched healthy controls using psychometric testing, subjective and objective sleepiness tests and the Balloon...

Ethical review	Approved WMO
Status	Pending
Health condition type	Sleep disturbances (incl subtypes)
Study type	Observational non invasive

Summary

ID

NL-OMON31051

Source
ToetsingOnline

Brief title
Decision-making in narcolepsy

Condition

- Sleep disturbances (incl subtypes)

Synonym
Narcolepsy

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: addiction, decision-making, narcolepsy, risk taking behaviour

Outcome measures

Primary outcome

Questionnaire scores

BART score

PVT mean Reaction Time

Secondary outcome

None

Study description

Background summary

Narcolepsy is a neurological disorder characterized by excessive daytime sleepiness associated with cataplexy and other REM sleep phenomena, such as sleep paralysis and hypnagogic hallucinations. Narcolepsy is caused by a loss of the orexin (hypocretin)-producing neurons in the hypothalamus. Loss of this peptide is sufficient to produce narcolepsy as mice, rats, and dogs with disrupted orexin signaling have all the major features of narcolepsy.
The orexins are two peptides, orexin-A (hypocretin 1) and orexin-B (hypocretin 2) generated from a single precursor and synthesized by a small number of neurons restricted to the lateral hypothalamus and perifornical area. Orexin-producing neurons project throughout the CNS, directly exciting monoaminergic and cholinergic neurons in the locus coeruleus, raphe nuclei, and basal forebrain regions. These targets play critical roles in attention, cognition, and the regulation of sleep-wake behavior, and reductions in their activity may cause the sleepiness, cataplexy, and other symptoms of narcolepsy.
Recent studies suggest the orexin/hypocretin system also plays an important role in reward processing and addiction. Drugs of abuse and other stimuli are rewarding because they increase release of dopamine into the nucleus accumbens (NAc). The main source of this dopamine is neurons of the ventral tegmental area (VTA). The orexin neurons heavily innervate and excite neurons in both the VTA and NAc, and orexin is implicated in the development of drug addiction (Harris). Specifically, orexin increases the excitability of VTA neurons by increasing their expression of glutamate receptors. In addition, orexin has

been shown to reinstate drug-seeking behavior in rodents in which this behavior has been previously extinguished. The importance of orexin in the amplification of reward signals is especially clear in mice lacking orexin, which show little or no addiction to morphine.
The above studies suggest that orexin may be critical in the development, maintenance and re-acquisition of addiction and reward-seeking behaviors in animals. The effects of orexin on addictive and reward-seeking behaviors in humans have not been studied. Narcoleptic patients, because of their low orexin levels, may have reduced activity in these VTA and NAc pathways. Specifically, they may be much less prone to risk and reward-seeking in their decision-making behavior. Support for this hypothesis comes from the clinical observation that while narcoleptic patients are often treated with highly addictive drugs including amphetamines, they rarely become addicted.
When considering orexin signaling in narcoleptic patients, it is important to distinguish narcolepsy with cataplexy from narcolepsy without cataplexy. Cataplexy is sudden muscle weakness brought on by strong emotions such as joking, laughter, or anger. It affects about 60% of patients with narcolepsy, either at the onset of sleepiness or within 3-5 years. Recent studies suggest that most narcolepsy patients with cataplexy have impaired orexin signaling. Approximately 90% of narcoleptic subjects with cataplexy (N+C) have no detectable orexin-A in their cerebrospinal fluid (CSF) even within a few months of symptom onset. In contrast, nearly all narcoleptic subjects without cataplexy (N-C) have normal CSF concentrations of orexin. Considering orexin*s implication in reward-seeking behaviors and addiction, it is reasonable to suggest that risk-related decision making behaviors in narcoleptic patients with cataplexy (low or absent CSF orexin) may be markedly different from those narcoleptic patients without cataplexy (normal orexin levels).
Our objective is to investigate decision-making in narcoleptic patients with and without cataplexy and compare it to that of age-and gender-matched healthy controls. The primary outcome will be measured by performance on the Balloon Analogue Risk Task (BART). Behavioral and personality studies have concluded that the BART is a useful tool in the assessment of risk-taking. Riskiness on the BART is highly correlated with measures of sensation seeking, impulsivity and deficiencies in behavioral constraint, as well as with self-reported occurrence of addictive, health, and safety risk behaviors. In evaluating the decision-making behaviors of narcolepsy patients, it is important to distinguish biological causes of lower reward-seeking and addictive behaviors (such as lower CSF orexin levels) from behavioral causes such as fear of self-harm due to reduced vigilance and increased daytime sleepiness with narcolepsy, forcing patients to select physically safer behaviors. For this reason, the BART, administered on a computer, without any potential for physical harm, is an appropriate test for demonstrating risk and reward-seeking in the narcoleptics, as opposed to a more physical task.

Hypothesis:

We hypothesize that narcoleptic subjects with cataplexy will have lower scores on an array of psychometric questionnaires associated with reward-seeking and risk-taking behaviors, as well as on the BART, compared to narcoleptic subjects without cataplexy, which are expected to be similar to age-and sex-matched healthy controls.

Psychiatric disorders such as drug and alcohol abuse and dependence, compulsive overeating and pathologic gambling have been associated with abnormally high scores on the Zuckerman Sensation Seeking Scale and the Eysenck Impulsiveness Scale. In turn, high scores on the Zuckerman and Eysenck Scales were shown by Lejuez et all to be correlated with abnormally high BART scores. Enrolling subjects with the psychiatric diagnoses of drug and alcohol abuse and dependence, compulsive overeating and pathologic gambling is likely to yield BART score outliers and may falsely skew the averages in either the narcoleptic or control groups towards high risk-taking and mask real differences, attributable to CSF orexin levels alone.
Smoking has also been associated with producing significantly higher BART scores, however due to cross-cultural differences between the Netherlands and the US and high rates of smoking in both narcolepsy patients and healthy people in the Netherlands, we elected to match the groups for smoking behavior, rather than screen out potential subjects due to daily smoking. Every attempt will be made to match the amount of cigarettes smoked per day, in addition to matching for age and sex.
Performance on the BART and other tests could be altered by reduced vigilance, so we will measure subjective and objective levels of sleepiness using the Epworth Sleepiness Scale (ESS) and the Psychomotor Vigilance Task (PVT), respectively. We will correlate ESS and PVT scores with BART scores to examine whether reward-seeking is reduced by sleepiness and diminished vigilance.

Study objective

Our objective is to investigate decision-making in people with narcolepsy with and without cataplexy and compare it to that of age-and sex-matched healthy controls using psychometric testing, subjective and objective sleepiness tests and the Balloon Analogue Risk Task (BART).

Study design

Methods:
Following telephone screening for inclusion and exclusion criteria, subjects will be educated about the purpose of this study, and informed consent will be obtained if they agree to participate.

Part I - Behavioral Screen Questionnaires:
(All Questionnaires are provided in the Appendix Section)
Following informed consent, subjects will be asked to complete the following

tests to study their risk-taking propensity:
The Zuckerman*s Sensation Seeking Scale(17) - Subjects are asked to choose between a total of 72 pairs of contrasting statements. The Zuckerman Sensation Seeking Scale is widely used in psychological studies for evaluation of Sensation Seeking, Thrill and Adventure Seeking, Experience Seeking, Disinhibition and Boredom Susceptibility.(13-16). The Sensation Seeking Scale stratifies screened subjects into high, moderate, and low categories for the behaviors mentioned above.
The Eysenck Impulsiveness Scale (18) - a 19-question Yes/No test that is a good measure of impulsive behavior across cognitive and behavioral domains and is widely used in psychological studies and correlated with substance and alcohol abuse (14, 16, 19). Eysenck breaks down results by age and sex. It is reasonable to consider individuals who score at or greater than 2 standard deviations above the mean Impulsiveness score for their age and sex as extremely impulsive.
Gormally*s Binge Eating Scale (BES), (20) - a 16-question test used in studies on eating behaviors to diagnose binge eating disorder. Typically patients scoring 17 or lower on the BES have been classified as non-binge eaters, those with a score of 18 to 26 as moderate binge eaters, and those scoring 27 or higher as severe binge eaters. (21, 22)
The World Health Organization-developed AUDIT (Alcohol Use Disorders Identification Test) screen - a 10-question screening tool, developed by the WHO, which has been designed as a as a simple and brief method of screening for excessive drinking. (23, 24)
The CAGE questionnaire for substance abuse - a 4-question tool widely used in primary care clinics as an initial screen for alcohol and substance abuse. (25, 26) CAGE is a mnemonic for a questionnaire that asks about attempts to Cut down on drinking, Annoyance with criticisms about drinking, Guilt about drinking, and using alcohol/substances as an Eye opener. Even though it was initially developed as an alcohol screening test, the CAGE questionnaire has been shown effective for screening of substance abuse. It is thought to be 60 to 90 percent sensitive when two or more questions are positive and 40 to 60 percent specific for excluding substance abuse (27).
Gamblers Anonymous*s 20 Questions (GA20) - a screening tool shown to be 98% sensitive and 99% specific for detection of problematic gamblers at the cut off-level of 7 or more positive questions. (28)
The Epworth Sleepiness Scale (ESS) - an eight-item questionnaire, used as a simple method for measuring daytime sleepiness in adults.(41)
Modified Edinburgh Handedness Inventory (EHI) - a 20-question handedness test, will be used to keep a record of handedness. (50, 52)

The above screens will be administered in random order. It is expected that subjects will complete all of the above screens in approximately 2 hours. A 15-min break will be given midway into Part I, after the first hour. Should they need it, subjects will be given extra time to complete these screens, as well as additional brief breaks. All questions should be answered in one visit, unless unforeseen circumstances arise.

*Specifically, scores of >=27 on the BES, >=8 on the AUDIT, >=2 on the CAGE and >=7 on the GA20 will be considered positive.

Part II - Balloon Analogue Risk Task (BART) and Psychomotor Vigilance Task (PVT), same visit as Part I:
Subjects will start with the Balloon Analogue Risk Task (BART)

1) Balloon Analogue Risk Task (BART)
Instructions about the Balloon Analogue Risk Test (BART) and about use of the computer and mouse (if needed) will be provided. Subjects will then be asked to sit down at a computer in a comfortable environment and take the BART
The Balloon Analogue Risk Task (BART) is a behavioral measure of risk taking that has convergent validity with real-world risk related situations (13). Performance on BART has been correlated with occurrence of real-world risk behaviors such as substance abuse, risky sexual behaviors, delinquent behaviors, as well as self-report measures of risk-related constructs such as sensation seeking, impulsivity and deficiencies in behavioral constraints (14-16).
The BART is a computerized task that simulates a balloon being inflated by the participant with the click of a mouse. The whole test can be performed in less than 15 minutes. During the task, the following items are displayed on the computer screen: a balloon and a bar that the participant clicks on using a computer mouse to inflate the balloon (labeled *Press this button to pump up the balloon*), a button with the label *Press to Collect $$$* that begins the next trial, a box that displays the total amount of money earned (labeled *Total Earned*), a box with the amount of money earned per pump, and a box that displays the amount of money earned on the previous balloon (labeled *Last Balloon*).
The task begins with a deflated balloon and includes 30 total trials (balloons). At any point, the participant can use the mouse to press the *Press to Collect $$$* button and take the amount of money accumulated from the current balloon and add it to their total earnings. Pressing this button begins the next trial with a new, deflated balloon. If the balloon explodes before the participant pressed the *Press to Collect $$$* button, the money earned from that balloon is not added to the total earned. Instead, that money is lost.
Each balloon has a different explosion point. Therefore, the probability of losing the money, as well as the potential loss, increases with each pump (13).
Subjects will perform the BART twice. Each time they will be presented with 30 balloons. In the first trial they will earn 5 cents per pump, without any compensation. In the second BART trial, subjects will unexpectedly be told that they will be compensated a monetary amount equal to their on-screen total BART earning.

NOTE: Reasonable effort will be made to test all subjects in the morning, when narcoleptic patients are typically most alert.
Subjects will be given a 5-min break following the BART and will be encouraged

to stretch and move around to prevent sleepiness.

This part should take less than 30 minutes.

2) Psychomotor Vigilance Task (PVT)
The Psychomotor Vigilance Task (PVT) is a reliable test of behavioral alertness, which consists of a series of reaction time (RT) measurements, usually performed over at least 10 minutes and designed to evaluate the ability to sustain attention and respond in a timely manner to salient signals (42). The PVT will be performed using the LUMC computer version of the PVT task. The subjects are asked to press the space bar as soon as they see a counter running on the screen. The RTs are measured and recorded for a pre-specified period. The test will last for 10 minutes as RT*s in narcolepsy patients tend to decline with time.

This part should take less than 15 minutes.

At the end of Part II, subjects will be compensated $50 for their participation, as well as the equivalent of their earnings on BART #2, in an effort to encourage greater risk-taking on the BART.

Study burden and risks

No risk, 4 hours in hospital (2 hrs questionnaires, 1 hr computer tasks)

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Age 18-64 years
Normal or corrected vision with acuity up to 20/60
Presence of Narcolepsy WITH or WITHOUT cataplexy, diagnosed by a neurologist experienced in Sleep Medicine
• Definite narcolepsy present for at least 6 months

Exclusion criteria

Change in narcolepsy medication in the last month
Recreational drug use in the past week
Diagnosis of substance or alcohol abuse or dependence - DSM-IV criteria
Diagnosis of gambling addiction
Diagnosis of binge-eating disorder
Diagnosis of uncorrected visual problems with acuity less than 20/60
Current diagnosis of generalized anxiety disorder, depression or other psychiatric illness
Other acute, unstable medical conditions or serious chronic diagnoses
Administration of any investigational drug within 5 half-lives of the drug prior to screening

Study design

Design

Study type:	Observational non invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Basic science

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-03-2007
Enrollment:	45
Type:	Anticipated

Ethics review

Approved WMO

Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL16677.058.07