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Research applications of a coordination ability test system (CATSYS) during 30 years

John Heebøll, Per Grove Thomsen, Finn Gyntelberg

ABSTRACT

The coordination ability test system (CATSYS) was invented in 1986 with the aim of using it for diagnosing neurological disturbances in people who had been exposed to neurotoxic substances in particular organic solvents. In this brief review, all articles where CATSYS has been used for scientific purposes have been retrieved and read. Articles on neurotoxicity and Parkinson's disease (PD) have been reviewed and referred to. The CATSYS measures hand prono/supination, finger tapping, tremor, reaction time and postural stability. The CATSYS has been used in environmental medicine among people exposed to mercury in food, and in employees exposed occupationally to mercury. Both a decrease in coordination ability and increased tremor has been observed in occupationally exposed groups, but not among people exposed to mercury in food. Similar observations have been seen with regard to manganese exposure where people exposed to manganese from environmental air pollution had no or minor effects in contrast to some occupationally exposed groups. In a few studies on use of alcohol and tobacco a tendency of increased tremor among smokers was observed, and have reduced postural stability among regular users of alcoholic beverages. The CATSYS has been found a useful tool in differential diagnostics between PD and familial essential tremor. CATSYS has been used in many scientific studies globally and has proven its value in research. Potentially, it may be instrumental for clinical purposes in particular in PD.

Keywords: Coordination test, Data acquisition, Environment pollution, Equipment, Neurotoxicology, Organic solvents, Tobacco, Tremor analysis

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BACKGROUND

The CATSYS was invented in the winter of 1986. The idea to make a computerized based system for measuring human coordination function raised from the use of some simple manual tests used by Mikkelsen for his thesis on building painters exposed to organic solvents [1]. The simple tests were used together with psychometric tests and Mikkelsen showed that the exposed painters performed less well both in these and the coordination tests compared to a control group of bricklayers.

During 1986 the first version of CATSYS was developed and tested in men and women without any known neurological disease or neurotoxic exposure. The first results demonstrating the feasibility of CATSYS were published in 1990 [2]. The complete developed CATSYS underwent standardization by Despres et al. in 2000 [3]. This complete system included the following coordination tests:

Finger tapping

This was carried out with the subject tapping the index finger on a small ten centimetre diametric box following a rhythmic sound that increased its frequency until the subject had to give up following the rhythm, following a rhythmic fixed frequency sound to test rhythmic control and an increased frequency beat to test maximum controlled action .

Prono-supination

This was carried out using the same pad as for finger tapping, and also following a fixed and an increasing rhythm as described above.

Tremor

Tremor of the hands was recorded with the test subject holding a stylus like a pen in front of the subject's navel. Frequency and-power of the tremor was recorded.

Postural stability

Stability was recorded with the test subject standing on a 35x45 cm platform containing three force sensors. The track of the intersection between the horizontal force plate plane and the vertical line through the subject centre of gravity recorded for 76 seconds with the subject having open and closed eyes.

Technical description

The CATSYS test system comprises a data logger and four sensors.

In principle, the data logger converts analogue sensor signals to digital numbers that are transmitted to the computer for further data processing. Technically, this is a so-called AD conversion. The digitized numbers are 8 byte long and the conversion frequency (sample frequency) is 32 Hz.

The postural stability plate generates three signals, each representing the vertical load on the supports, when a subject is standing on the plate. The three forces are used for calculating the force center, which is the intersection between the force plate and a vertical line through the subject's center of gravity. Dynamical effects are disregarded since the subject movements are very small and of low frequency. The force center coordinates will change as the subject keeps in balance during the recording period. The recording drum is 8 cm flat capsule with an acoustic microphone mounted inside. When a finger tap or a hand slap is hitting the capsule, the microphone will generate a small electrical voltage. The data logger amplifies this signal, and when the amplified signal from the microphone exceeds a certain predefined level, this is perceived as a hit. The data logger internal watch will register the time for this event as well as the time for the trigger event (the metronome beat – or the beep, that the data logger loudspeaker emits) and send the paired time measurements to the computer. Thus, we obtain a series of stimuli and action times – or occasionally stimuli with no action following due to subject failing to act.The microphone can be turned on and off during a test. It is turned off immediately after a hit – to avoid multiple hits stemming from the same action being recorded. Further, the active period when the microphone is turned on around a stimulus decreases with increasing metronome frequency. This makes it increasingly difficult for the subject to follow the metronome when the frequency increases, and hence the moment when coordinated hitting expires and goes into chaotic slapping is quite conspicuous, leading to a good reproductivity in maximum frequency determination. The reaction time sensor is a simple switch activated via a handle hold by the subject. Paired stimulus and action times are determined and transmitted to the computer.

The tremor sensor is a sophisticated analogue device that measures accelerations at the tip of the sensor and perpendicular to the sensor tube, in an X and a Y direction. The signals are converted into bytes that are streamed real-time to the computer. The signals are processed state-of-the-art to present the tremor pattern in the frequency domain – that is: a normalized spectrum indicating the amount of energy being used for generating the tremor in each of a number of frequency bands (272) between 0.8 Hz and 15 Hz, as well as the RMS of power being applied to drive the tremor during the measuring period (typically 8 seconds).

The spectrum is very sensitive to any disturbance of normal human rest tremor making this test sensitive to subtle impacts on the part of the human neurological system, which generates and controls rest tremor.

The sensors and the data logger are shown in the Figure 1. To the left is the force plate. Next to it the reaction time handle bar. A bit forward to the right of this: the "drum" or the touch sensitive capsule. Last to the right is the tremor sensor: We call it a tremor pen, and behind it: the data logger.

The computer software allows comprehensive user adaptability as well as data base facilities and – management, making the system a flexible research instrument.

Further, a number of export facilities have been developed to allow safety copying, export into statistical database systems and print outs for patient files on paper etc.

Figure 1: The computer software allows comprehensive user adaptability as well as data base facilities and management, making the system a flexible research instrument.

METHODS

The literature search on which this review is based was carried out using the databases PubMed and Google Scholar. The publications where CATSYS has been used for research within neurotoxicology, tremor and Parkinson's disease (PD) are referenced in the present review. Only studies where CATSYS has had a role where its use could be evaluated were included in this short review.

Applications in neurotoxicology

Mercury

The first publication where CATSYS used was in a group of 38 Danish workers where 14 had been exposed to a major spill of mercury. The 38 workers were divided into two groups, a high and a low exposed group. The high exposed group had urine mercury values on average above 100 nmol/L and the low exposed group on average below 10nmol/L urine. The high exposed group had reduced coordination ability and more tremor than the low exposed group a difference also seen after 3 and 16 months of follow-up [4].

Two later publications did not find any statistical differences between groups with mercury exposure compared to unexposed groups validated with determination of urine mercury values. An Italian paper comparing 22 subjects living in the island of Caloforte (SW of Sardinia) was compared with 22 age and sex matched controls working in a chemical factory in Sardinia. Neither of the two groups had been exposed to mercury occupationally. The Caloforte group had been consuming tuna fish with rather high mercury content for many years. Subsequently, they had urine mercury levels on average 6.5 μg/g creatinine versus 1.5 μg/g creatinine among the controls. No significant differences with respect to tremor was observed between the two groups, but the Caloforte group had a lower performance with respect to finger tapping [5].

A more recent study on mercury exposure supports the results of the Caloforte study. A Canadian study on 43 chlor-alkali workers and 22 age and sex matched non-exposed controls did not find any differences in tremor tests between the two groups even though the workers had eight times higher mean urine mercury values. The urine levels were at the same levels among the workers as observed in the Caloforte population.

The authors of this review know some further results on mercury exposure where CATSYS has been used, however from unpublished university student reports. CATSYS has been used among gold miners in Brazil and in the Philippines. In both these studies mercury exposed gold miners had more abnormal CATSYS results than non-exposed controls, and more tremor.

Manganese

The CATSYS has also been used in people exposed to manganese both occupationally and in the environment. A recent publication from Ohio tried to evaluate motor function in order to asses the effects of long-term, low level environmental manganese exposure in residents of an Ohio community where a large ferro-and silico-manganese smelter had been active for more than fifty years. Manganese exposure was assessed using modeled airborne manganese and blood manganese in one hundred residents from the manganese-exposed Ohio and in 90 non-exposed controls. The sway-test included in CATSYS was used together with questionnaires and the unified Parkinson's disease Rating Scale (UPDRS). The manganese-exposed group performed less well than the controls, however, the authors concluded that manganese as the cause was unlikely, and no clinical cases of manganese intoxication was observed [6].

A Norwegian study on 96 welders exposed to manganese (Mn) in welding fume were compared to 96 age matched referents. Associations between both B-Mn and air Mn and Digit Symbol and Finger Tapping were observed. The welders performed poorer in the Finger Tapping test, which was also the case among 27 patients who had been compensated for manganese intoxication. The patients, however, did not have tremor using the CATSYS tremor test [7].

A Danish prospective study on 60 steel workers from a Danish steel plant where all of them had been exposed to manganese and with blood manganese values around 150 nmol/l found that after a ten-year period of observation the exposed workers showed a decline in the ability to perform fast finger tapping and fast hand pronation/supination. However, no statistical significant associations between the degree of manganese exposure and decline in performance was found [8].

A prospective study in a group of 43 confined space welders, (mean age 47) who had been exposed to high manganese concentrations in the air during 16.5 months

period were examined at baseline and 3.5 years after exposure. These welders had decreased psychomotor speed and more dominant hand tremor and body sway than at baseline [9].

Alcohol, smoking and medicine

A Canadian publication used CATSYS in an experimental exposure chamber study to find out if ethanol added to gasoline might have influence on neuromotor effects in connection with refuelling. Five healthy non-smoking adult males were exposed to ethanol in their breathing zone for six hours (0, 250, 500 and 1000 ppm.) All underwent a full CATSYS test. No differences were observed during exposure or non-exposure, making the authors to conclude that acute exposure to inhalation of ethanol at 1000 ppm or lower is not likely to cause any significant motor alterations in healthy males [10].

A Danish cross-sectional study on 686 subjects who had been deployed in Iraq after the first gulf war and 231 control subjects found that no differences between the veterans and the controls were found with respect to performance in all the CATSYS tests. A result that could lead to a conclusion that chemical exposure at a relevant level to induce neurotoxic effects was unlikely among the veterans. However, the sway test revealed that men drinking more than 35 gram of alcohol a day swayed more than those who had lower alcohol consumption. It should be mentioned that the test took place in the morning and the participants were told not to drink alcohol for many hours before the test [11].

A Norwegian study on 49 smokers/snuffers and 49 non-smokers/ non-snuffers found that smokers/snuffers had more hand tremor and a different tremor pattern than non-smokers/non-snuffers in particular with increasing age [12].

A Danish study carried out on 76 female day-case patients undergoing minor gynecological operations were assigned at random to the anesthetic agent used, propofol 2.5 mg/kg or thiopenthone 4 mg/kg. The following CATSYS tests were used: Finger pointing on a screen (first edition of CATSYS), reaction time test, finger tapping and hand prono/supination [13]. The tests were conducted once before the operation and one and two hours after awakening. Postoperatively, the initial impairment and the subsequent regression towards the preoperative test results were very similar independent of which of the two anaesthetic drugs, that was used. The test apparatus was able to detect even minor differences [14].

Quite recently CATSYS was used measuring swaying after laparoscopic gynaecological surgery in order to evaluate if discharge from hospital two hours after surgery was safe enough, this was the case [15].

Tremor and Parkinson`s disease

Tremor is the most common movement disorder either essential or caused by Parkinson`s disease (PD). The aim of a Hungarian study was to determine if CATSYS might be helpful in the differentiation between PD and essential tremor. Three groups were studied a group of healthy controls (n=18), a group with PD (n=39) and a group with essential tremor (n=37). All underwent the full CATSYS programme. Tremor intensity, median frequency and frequency distribution showed characteristic differences in the three groups. Performance in fast alternating movements of hands and fingers were significantly worse in both tremor groups compared with the healthy controls. Differences in tremor pattern differed more between right and left hand among the patients with PD, so the authors concluded that their results helped to differentiate PD from essential tremor as well as predict disease course and the effect of therapy [15].

The effect of sub thalamic nucleus deep brain macro stimulation (STN-DBS) was monitored with CATSYS as a supplement to short-time clinical observation and considered very useful in a pilot study on 12 consecutive PD patients, who received staged unilateral STN-DBS implants. Ten normal controls were included in which results revealed excellent test-retest reliability for postural tremor. The treated patients improved both with respect to tremor and finger tapping on their treated side [16].

With the primary objective to provide technical guidance for the use of CATSYS in PD, 44 patients with idiopathic PD and 28 healthy controls were prospectively recruited and all underwent a full CATSYS test. CATSYS discriminated between PD and controls on measurements of rest/postural tremor, prono/supination, finger tapping, simple reaction time, and postural sway intensity and velocity. CATSYS was associated with relevant clinician- rated unified Parkinson's disease rating scale (UPDRS) items assessing tremor and bradykinesia [17].

A Canadian study used the postural sway test in early PD before and after regular oral levodopa dosing. Mild baseline subclinical changes in postural sway were observed in the patients, changes that were modulated by dopamine [18].

A Hungarian study used the CATSYS tremor test to analyse the tremor pattern in a number of patients with essential tremor and PD. It was found that both among patients with essential tremor and PD, tremor was significantly asymmetric, while frequency and frequency dispersion were symmetric in essential tremor patients but asymmetric in PD patients. The authors concluded that this method might be used for differential diagnosis between the two conditions [19].

Another Hungarian study in 15 patients with epilepsy and 14 controls aimed at detecting objective signs of deterioration of motor performance in the epilepsy patients treated with valproate during long-term. A full CATSYS test showed that the treated patients had irregular repetitive hand and finger movements, and that maximum frequency of repetitive movements was significantly lower in the group treated with valproate compared to controls. No difference with respect to

tremor or reaction time was seen. The authors concluded that objective methods might help to detect valproate-induced motor performance deterioration, also in patients without complaints [20].

A Hungarian study using the CATSYS tremor test could objectively demonstrate improvements in tremor after ablations or deep brain stimulation in PD patients treated with these methods [21].

Farkas et al. hypothesised that regularity of rhythmic movements in essential tremor (ET) is impaired and that cerebellum is involved in the pathomechanism of ET. To test this using CATSYS finger tapping and prono/supination tests following a rhythm, the authors found that variability was significantly higher compared to a group of healthy controls. Timing of rhythmic movements of the two hands was disturbed to the same degree. The conclusion was that the observations supported the hypothesis.

Using the CATSYS tremor test Scanlon et al. studied the properties of tremor in the lower limbs in 16 PD patients and 8 controls. They found that intraindividual variability of rest and postural tremor frequency in the dexterity-dominant lower limb was lower in the PD patient than in the controls. Also the rest tremor frequency was discrepant between upper and lower extremities in the PD patients. The authors conclude that objective measurement of tremor may improve our understanding of lower limb motor dysfunction in PD, and be useful in diagnostics [22].

Evaluation of the method

In supplement to the papers mentioned above the PhD thesis of Kato Rand should be mentioned. This thesis was based on the very first edition of CATSYS that did not include the swaying and tremor test, but a finger-pointing test not included in the newer CATSYS. Kato examined 600 men and women, and found that this first edition was reproducible, that older people performed a little slower than young people but very little. Men had slightly shorter reaction times than women, and men with compromised concentration ability after long-term solvent exposure were slower and less precise [23].

Fragile-X spectrum disorders

During the last years CATSYS has been used by researchers dealing with Fragile-X genetic disorders. Both postural stability and tremor ataxia in patients with these disorders have been found useful for diagnostic purposes [24, 25].

Alcohol intake confounding neurotoxicology.

Recently, a Norwegian study on manganese exposed welders found that welders not drinking alcohol had no tremor using CATSYS in contrast to welders habitually drinking larger amounts of alcohol. Alcohol consumption was assessed by measuring serum carbohydrate deficient transferrin (sCDT) [26].

Hand-arm vibration-exposure (HAV)

A recent Swedish study used CATSYS to measure tremor in 178 male workers with or without exposure to HAV. No association between HAV and tremor was observed, however, tremor was positively associated with age and nicotine use [26].

CONCLUSION

To the authors of this review, being also the inventors and developers of coordination ability test system (CATSYS), it seems quite reassuring that CATSYS has proven its value in studies both on toxicity and within PD research. The usefulness demonstrated in the papers on Parkinson's disease validates the results obtained in the toxicological studies within occupational and environmental medicine. Until now the development has been a non-profit enterprise, but the research carried out during the last 30 years indicates, that CATSYS in addition to research purposes, might also become a useful tool in clinical practice in the future.

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Author Contributions

John Heebøll – Substantial contributions to conception and design and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Per Grove Thomsen – Substantial contributions to conception and design, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Finn Gyntelberg – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

In theory all three authors have a conflict of interest since we have been owners of a small company that has developed the CATSYS equipment and made it available to researchers all over the world. Hovever all surplus in the process has been used for development of the equipment and none of the authors have had any profit. The company is now closed.

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