



## Amphetamine exposure and dementia – A hypothesis of the long term sequelae of cognitive enhancers based on opponent process theory

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### ARTICLE INFO

#### Keywords:

Amphetamine  
Cognitive enhancer  
Dementia  
Opponent process theory

### ABSTRACT

Dementia is a cluster of brain dysfunctions with a characteristic of progressively debilitating in individuals' ability of operating cognitive functions and that affects seriously to patients' daily life. We presented a hypothesis in this article that earlier exposure of a common used cognitive enhancer amphetamine may lead to individuals to be more liable to develop dementia in their later life based on the opponent process theory. The theory proposes that following a positive response, homeostatic changes in brain circuits may function to go opposite to the positive response, thus a cognitive deterioration may incur in later life in the individuals who exposed to amphetamine earlier. Along with the hypothesis, amphetamine is also highly associated with the working hypothesis updated for dementia in terms of beta-amyloid cascade, tau protein, oxidative stress and neural inflammation. Finally, we presented two practical methods to evaluate the hypothesis. In non-human approach, rat model of amphetamine dependence would be employed together with evaluations of behavioral performance of memory test and neurochemical markers associated with oxidative stress. In human approach, a matched-cohort design observational study would be highly recommended.

### Introduction

Dementia is serious mental dysfunction consuming vast society resources and with great concerns and challenges in contemporary medicine [1]. The disease refers to a progressive and overwhelming brain function deterioration as shown by worsening of multiple aspects of cognitive performance, which can be observed in both vascular and non-vascular features, for example, in cerebral hypoperfusion [2], and sabotaged function of neuronal communication (ie., a downward transmission of synaptic chemicals, [3]), respectively. This characteristic indicates that dementia, no matter its classification in term of nosology, is a disease of a devastating downgraded functional change of brain. Mechanisms of this overall downward tendency can be complicated. Great effort has been made not only to work out the mechanism behinds this age-dependent cognitive deterioration, but also to identify if there has any possible predisposing factors beforehand. In other words, risk factors leading to cognitively deterioration afterwards should be thoroughly examined in order to provide a better strategy for the prevention of dementia.

Opponent process theory was first introduced by Solomon and

Corbit [4,5] and elaborated later by Koob and Le Moal [6,7]. It suggests that following a positive response (usually referring to an above-baseline with upward change of hedonic level, *a-process*), homeostatic changes in brain circuits may then exert to dampen the positive response (i.e., causing a downward change below baseline, *b-process*). In terms of drug addiction of central stimulants, the compulsive drug consumption can be viewed as a negative reinforcing course to compensate the *b-process*. Usually the *a-process* occurs rapidly after the use of the drug. As to the *b-process*, it goes with a slow onset and in its process the body exerts to achieve homeostasis through change, in which the accumulating brain damage resulting from this chronic aberration as time goes by refers to an allostatic load [8].

In this regards, the exposure of central stimulants, usually being highly abused as short term cognitive enhancers [9,10], may be regarded as one of the leading factors to cause dementia based on the opponent process theory. Thus, if we widen the time scale to a life-long period and consider earlier use of amphetamine as a exposure of cognitive enhancer which causes upward change of cognition in the beginning (*a-process*), it is possible that the *b-process* occurs years later in a quite procrastination manner as the abusers are getting older and

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reflects its serious allostatic load on a downward change of cognition from the baseline. In other words, for those experiencing earlier amphetamine exposure, the cognitive deterioration can be viewed as a specific form of compensatory change of brain function following the exposure of cognition enhancer, such as amphetamine, thus renders a high risk of development dementia.

In addition to serve as a cognitive enhancer to be the prerequisite of cognitive inactivation later in terms of the opponent process theory, amphetamine is in fact considered a candidate risk factor contributing to the development of dementia lies in its strong association to the biological substrates implicated in the development of dementia with multiple but crosstalk-manner mechanisms (primarily for Alzheimer type) including beta-amyloid cascade, tau protein, oxidative stress and neural inflammation [11,12]. Increasing evidence shows that exposure of methamphetamine (N-methylamphetamine, a more dangerous form of amphetamine) promotes the formation of A $\beta$ 42, one of the key Alzheimer's disease-like pathological proteins [13], increases the expression of the tau protein [14], produced greater dementia-related oxidative stress markers including catalase (CAT) and methane dicarboxylic aldehyde (MDA) [15]. Amphetamine is also among chemicals with the characteristic of overproducing reactive oxygen species (ROS), referring to a greater oxidative stress, has also been suspected about their risk of developing Alzheimer's disease, and this concern has been raised as early as 2001 in this journal (i.e., Medical Hypotheses [16]). Finally, methamphetamine may modulate the functions of immune cells and change the cytokine balance, which leads to neurotoxicity with compromise of the blood-brain barrier and alterations to brain plasticity and eventually contributes to age-related dysfunctions, including dementia [17].

We therefore hypothesize that early amphetamine exposure may increase the risk of developing dementia in later life. As this hypothesis can be practically tested in both human and non-human approaches and directly targeting at the mechanisms addressed above, it would provide useful information towards a more comprehensive understanding of the development of dementia. If we confirm that early exposure of amphetamine may enhance the risk of developing dementia, it certainly goes beyond its current clinical implication, from the interpretation of stimulant-induced drug dependence (based on dysfunction of dopaminergic transmission) to a new utility to serve as a working hypothesis (based on opponent process theory) to interpret the development of cognitive degenerative disease. We now formulate the hypothesis as following with suggestion how to examine and evaluate the hypothesis.

## Hypothesis

The hypothesis addressed here is an elaboration of what is mentioned above, with a practical justification regarding how to associate central stimulants and dementia. We hypothesize that early exposure of amphetamine, particularly in those of amphetamine dependence, may enhance the risk of developing dementia afterwards.

## Evaluation of the hypothesis

### *Establishment of rodent model of early amphetamine exposure and to examine its association with cognitive deterioration in later life*

Amphetamine is quite often used in rodent experiments in the studies of drug dependence [18], neurotoxicity [19], and psychotic disorder associated to central dopaminergic dysfunction, including schizophrenia [20,21]. To induce amphetamine dependence in rodents, self-administration of methamphetamine in a schedule of reinforcement is the most reliable and well acknowledged protocol [18,22]. Rats would undergo surgery for implantation of catheters into their jugular vein [23]. After a period of recovery time (usually 7 days), self-administration training would be initiated in which rats are reinforced by

amphetamine once they are instrumentally conditioned [24]. In terms of justifying the validity of dementia, impairment of spatial learning and memory ability in rats can be assessed by Morris water maze task [25] and novel object recognition task (NORT, [26]). Cross talk between phosphorylated tau protein and dementia-related oxidative stress markers such as CAT and MDA can be measured as biological indexes to support the behavioral data.

There are two levels of hierarchy to investigate the association between dementia and early exposure of amphetamine. The first one is grossly to examine whether the amphetamine dependent rats would go to cognitively deteriorated when they are getting older (usually at 20 months after birth, equals to 60 years old of human being, [27]) when compare with normal controls. If the result is encouraging, it can be then extended for a further step to clarify whether the strength of the dependence correlates to the degree of cognitive deterioration, i.e., the higher the dependence develops, the greater chance these rats become cognitively demented when they are old. The latter is useful to examine the hypothesis if the brain is stimulated to a greater extent, it becomes inactivated or deteriorated more, thus to see what the opponent-process theory [5,28] suggested would eventually occur.

### *Establishment of human study of early amphetamine exposure and to examine its association with cognitive deterioration or dementia in later life*

In human approach, a cohort designed observational study via big data analysis is suggested to –examine our hypothesis because a long-term inspection time is required. In fact, a more suitable way is to launch a nationwide, retrospective matched-cohort design study to investigate that among those with the history of amphetamine exposure, how many or what percentage of them are diagnosed with dementia later on. Practically speaking, the study should aim to clarify the association between risk of dementia in subjects with amphetamine-related disorder and non-amphetamine-related disorder cohort based on categorical system of *International Statistical Classification of Diseases and Related Health Problems* (ICD). The follow-up period should be as long as possible, often over a 15-year period. If it is possible, information would be best obtained from longitudinal health database of that nation. All participants of the study should be followed from the index date until the onset of dementia including Alzheimer dementia (AD), vascular dementia (VaD), and other degenerative dementia.

To eliminate the confounding factors which cause problem in interpreting the data, covariates should be considered to the analyses too, including sex, age, education, geographical area of residence, urbanization level of residence, levels of hospitals as medical centers, regional hospitals and local hospitals, and insurance premium. Furthermore, Charlson Comorbidity Index (CCI) is suggested to analyze the comorbidities categorized by the ICD codes, thus can score each comorbidity category, and combines all the scores to calculate a single comorbidity score [29].

Finally, it should be cautious to employ opponent process theory in interpreting the pathoetiology of dementia, as the theory may not be appropriate when applying to other cognition-disrupted agents with the associations of oxidative stress and neural inflammation. For example, alcohol is acknowledged risky to cause cognitive impairment in a deteriorating manner, yet alcohol is considered a central nerve system depressant, rather than stimulant. It is thus difficult to explain the role of alcohol in cognitive deterioration with opponent process theory. It is still in debating whether the cognitive impairment in alcohol-related dementia (ARD) is due to direct ethanol neurotoxicity, or representation of another underlying pathology (for example, thiamine deficiency) [30]. Accordingly, as dementia is a cluster of disorders with multiple mechanisms and high heterogeneity of neuroanatomical patterns [31], substances to damp central nerve system may function differently than that of central stimulants in causing cognitive impairment.

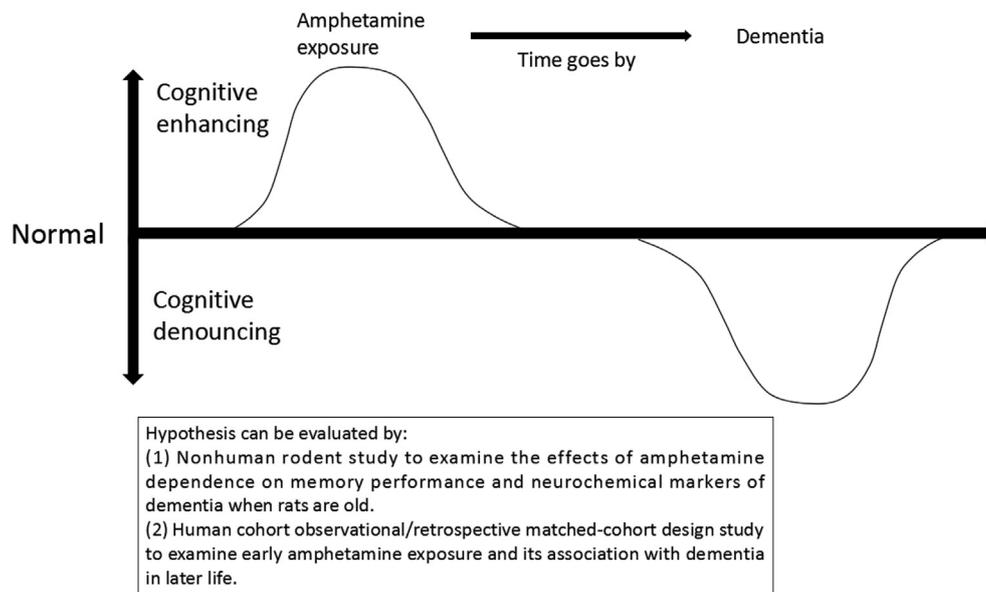


Fig. 1. Schematic illustration of opponent process theory in interpreting the association from amphetamine exposure to dementia.

## Conclusion

In summary, we hypothesize that earlier amphetamine exposure may cause the individual to be more liable to develop dementia when they are old. It is not only because that amphetamine serves as a cognitive enhancer which is the prerequisite of cognitive inactivation later on according to the opponent process theory, but also amphetamine associates considerably to the biological substrates involved in the crosstalk mechanisms implicated in the dementia. The hypothesis can be evaluated practically in both non-human and human approaches. Our hypothesis and the evaluation strategy are now graphically presented in Fig. 1.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.mehy.2019.109327>.

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