

Cognitive Processes to Understand Alcohol Use Disorder

Summary of Ph.D. thesis

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Original research articles related to the thesis

- I. Mátyássy A, Kéri S, Myers CE, Levy-Gigi E, Gluck MA, Kelemen O. (2012)** Impaired generalization of associative learning in patients with alcohol dependence after intermediate-term abstinence. *Alcohol Alcohol.* 47(5): 533-537
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- II. Mátyássy A, Kelemen O, Sárközi Z, Janka Z, Kéri S. (2006)** Recognition of complex mental states in patients with alcoholism after long-term abstinence. *Alcohol Alcohol.* 41(5):512-514.
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Selected abstract related to the thesis

- I. Mátyássy A, Kéri S, Myers CE, Gluck MA, Kelemen O. (2011)** Impaired generalization during reinforcement learning may indicate hippocampal dysfunctions in patients with alcoholism. (poster: P.6.a.001) ECNP Paris 2011. 10.06. (abstract: *Eur Neuropsychopharmacol.* 21, (Suppl. 3), 2011, p. S560)

Selected publications closely related to the thesis

- I. Mátyássy A. (2002)** Farmakoterápia az addiktológiában. *Családorvosi Fórum.* 11: 4-12.

- II. Kelemen O, Mátyássy A, Kéri S. (2004)** A ventromedialis prefrontalis kéreg szerepe addiktológiai kórképekben. *Clin Neurosci. (Ideggy Szle.)* 57:4-10.

- III. Mátyássy A, Szűcs A. (2005)** Alkoholfüggőség - társuló hangulat - szorongásos zavarok. *Addictol Hung. (Addiktológia)* 4(3): 297-318.

- IV. Mátyássy A, Kelemen O. (2011)** Az alkohol okozta mentális és viselkedési zavarok. In: *A pszichiátria rövidített kézikönyve (szerk.: Németh A, Füredi J), pp. 187-212. Medicina, Budapest.*

1. Introduction

Cognitive psychology represents useful approach for understanding clinical psychiatric conditions. It is also an important tool to understand the neuronal foundation of alcohol use disorder (AUD), promises the discovery of a possible endophenotype and could help to create proper pharmacological and psychological treatments (Bernardin et al. 2014; Fein et al. 1990). Then again, identifying brain processes and related cognitive dysfunctions resulting in an increased vulnerability for AUD may provide a possibility to recognize AUD at an earlier stage and as a consequence it could be important in creating better prevention programs too.

It is well known for a long time that alcohol is a neurotoxic agent that influences numerous cognitive processes, and it is also widely accepted that the abstinence period after alcohol cessation shows a gradual improvement of these functions (Fein et al. 1990; Crews and Nixon 2009). Therefore, in our research we focused in particular on memory functions and mentalization processes in an attempt to investigate patients after longer periods of abstinence (more than 6 months) to exclude the direct toxic effect of alcohol and allow a longer regeneration period.

The main goals of this work were to investigate the following:

- I. To examine the associative learning functions in intermediate-term abstinent alcohol dependence patients.
- II. To assess social cognitive functions by employing tests to investigate complex emotional recognition in intermediate-term alcohol dependence subjects.

2. Cognitive dysfunctions in people with alcohol use disorder

Alcohol use disorder (AUD) is one of the most significant problem in health related behaviour resulting in diverse mental and somatic consequences (Rehm et al. 2010). Alcohol misuse can change the functional connections of the brain and can cause direct neuronal damage resulting in cognitive dysfunctions. Even acute abuse of alcohol causes some reversible dose dependent mental disequilibrium. Long-term alcohol use leads to permanent damage, sometimes as extreme as Korsakoff-syndrome or alcohol-induced dementia. Fortunately, after discontinuation of alcohol abuse a cognitive recovery can be seen following a certain period of sobriety, so the duration of abstinence is essential when we investigate the effect of alcohol on the cognitive functions. At present the official terminology in the literature uses the following division: short-term abstinence - means less than 1 month; intermediate - means 2-12 months; long-term abstinence - means more than a year.

2.1. Learning and memory

Beside other neurocognitive damage, deterioration of the long-term memory processes is one of the most consistently reported impairment in AUD.

Contemporary research conducted on both humans and animals indicated that multiple interacting but dissociable memory systems exist in the brain. The basic distinction for long-term memory refers to implicit (procedural) and explicit (declarative) (Zola-Morgan and Squire 1993; Poldrack and Packard 2003).

Explicit (“declarative or overt”) memory refers to conscious recollection of facts and events. It is further divided into semantic and episodic subdivisions. Semantic memory is identified as concept-based and context independent category. Episodic memory is related to specific personal experiences, so it is evidently context dependent, and even the source of the memory trace is included within it. On the other

hand, the contents of implicit (“procedural or covert”) memory are inaccessible for conscious information processing. The medio-temporal (hippocampal) and diencephalic structures are candidate neuronal substrates for explicit memory. Implicit memory includes many diverse processes contained within different brain areas such as the sensory neocortex, basal ganglia, and cerebellum. Animal and human data supports the fact that the basal ganglia (BG) play a crucial role for gradual learning skills and habits. In addition, these processes are highly important because they are responsible for the development of reward dependent drug-seeking habits. Besides the classical stimulus response associative learning, the basal ganglia are crucial in sequence learning and category learning as well. The interaction of the two systems is critical, so although the medial temporal lobe (MTL) is not directly associated with stimulus–response learning, it has a major role in the generalization of previously learned information in a novel context.

A larger body of work and research is available in the investigation of explicit memory in AUD. AUD patients have diminished capacity to encode novel facts, have considerable slower learning processes and a specific vulnerability of the episodic memory subsystem as well. In relation to the accumulated and available psychological findings in AUD, many imaging data sets support the concept of severe damage of the MTL and related areas in this patient population (Oscar-Berman and Marinkovic 2003; Pitel et al. 2014).

In case of implicit learning processes, the animal studies emphasise cortico-basal ganglia-cortical loop pathways which play a pivotal role in reward and reinforced learning and Pavlovian conditioning being crucial in the development of dependency. However, limited results coming from human studies are available as regards testing special functions of BG in AUD population.

Also it is difficult to find studies investigating both BG and MTL dependent learning within the same task in AUD. This is important because basic differences

among the tests for implicit and explicit memory systems could result in questionable findings. For this reason, we had chosen a single test, the so called acquired equivalence learning test (RAELT: Rutgers Acquired Equivalence Learning Test, Myers et al. 2003) to investigate the possible memory impairment in AUD.

2.2. Social cognition

“Theory of Mind” (ToM) refers to a possibly unique human ability to attribute beliefs, intentions, and feelings to other persons. Recent research has demonstrated that ToM can be dissociated from other cognitive functions and is related to a relatively specialized social cognitive network in the brain, including the medial prefrontal and cingulate cortex, posterior superior temporal cortex, and temporal pole. Beside other task, mental states can be read from faces and eyes expressions. The Reading the Mind in the Eyes’ Test (RMET) uses fragments of facial and eye expressions of mental states (not mere basic emotions but complex mental status as well) from the part of the face around the eyes (Baron-Cohen et al. 2001). This is an automatic, unconscious evaluation without any learning tendency.

As meta-analyses indicate, the great majority of the available articles used the RMET test, suggesting RMET as a sensitive tool for research purposes in this area, and also recommended the usage of it in AUD.

Usual conclusions of the reviews were that lower mentalization performance is noticeable in AUD, and that longer duration of alcohol consumption and more severe depressive symptoms correlate with poorer performance.

2.3. Questions addressed by the thesis

The thesis addressed the following research questions:

1. Is the basal ganglia-dependent learning process affected in AUD after longer periods of (intermediate-term) abstinence? (Experiment 1; paper I).
2. Is medial temporal lobe-dependent learning impaired after a longer period of abstinence? (Experiment 1; paper I).
3. „Is there a correlation between explicit and implicit memory systems in this subject population? (Experiment 1; paper I).
4. Is there a ToM deficit in AUD after a longer period of abstinence? (Experiment 2; paper II).

3. Subjects and methods

3.1. Subjects

The patient group consisted of 20 subjects in Experiment 1 (Associative Learning: Fish) and 30 subjects in Experiment 2 (ToM: RMET) with DSM-IV alcohol dependence, participating in Alcoholic Anonymous (AA) groups. In the first place the inclusion criteria required abstinence for more than 6 months (average: 9.8 months, SD = 3.1) The patients did not receive any psychotropic drugs. To exclude unexplored depression symptoms that may have influenced cognitive functions we used a limit score of <10 on the Beck Depression Inventory (BDI).

3.2. Procedures

3.2.1. Experiment 1: The acquired equivalence associative learning task

The antecedent stimuli were four illustrations of faces (man, woman, girl and

boy). The boy and woman had blond hair while the girl and man had dark hair. Thus, each stimulus had three possible pairs related to 1) age (adult vs. child), 2) gender (male vs. female) and 3) hair colour (blond vs. dark). The consequent images were cartoons of fishes coloured red, orange, pink and purple. Two fishes appeared under the faces, but the position (left-right) randomly varied in each trial. The participant should press one of two separate keys labelled as 'LEFT' and 'RIGHT' to mark whether the fish on the left or the fish on the right was associated with the face. The chosen fish drawing was encircled and confirming feedback was given. When an incorrect response was given a sharp, alert beep sounded (Figure 1).

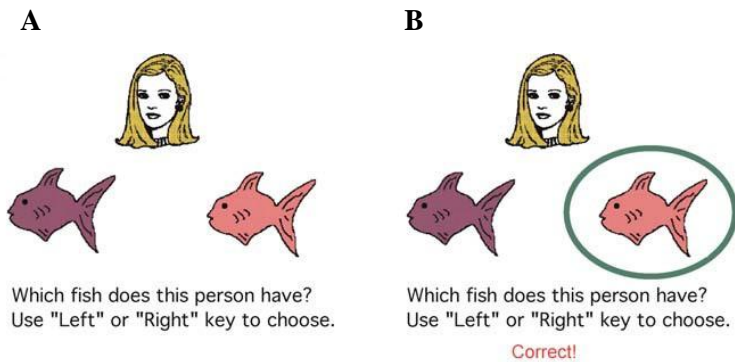


Figure 1. Example of an experimental trial.

First (A), stimuli (illustration of a face plus two fishes) appeared on screen. Second (B), the response of the participant was encircled and confirming/punishing feedback was given by the computer.

The acquisition phase included three stages. We used these many consecutive correct answers to make sure that the participant successfully gained the increasing number of associations from stage 1 to stage 3.

After completing the acquisition phase, they started the transfer phase, in which they did not receive any feedback. Beside the old associations there were new combinations for testing how s/he can use the learnt situations to solve the novel,

untrained settings (Table 1). This required that the participant can recall previously acquired associations and to generalize this knowledge to form new associations. (for methodological details, see Myers et al. 2003).

Table 1. The acquired equivalence associative learning task

Acquisition Phase			Transfer Phase:
Stage 1: Shaping	Stage 2: Equivalence training	Stage 3: New consequences	Equivalence testing
A1—X1	A1—X1	A1—X1	A2—X2 ?
	A2—X1	A2—X1	
		A1—X2	
B1—Y1	B1—Y1	B1—Y1	B2—Y2 ?
	B2—Y1	B2—Y1	
		B1—Y2	

During stage 1, participants learn the first 2 associations between different persons (A, B) and fishes (X, Y). During stage 2, different persons (A2, B2) are associated with the previously seen fish (stimulus equivalence), whereas, during stage 3, new consequences (fish X2, Y2) are added. During the transfer phase, participants are tested on the associations learnt in stages 1–3 (not presented in the table) and also on new associations that are not learnt during stages 1–3, but are the consequences of stimulus equivalence (Myers et al. 2003).

(In the table only the trials with the new associations are denoted)

3.2.2. Experiment 2: “Theory of Mind”: Eyes Test

The examiner presented 29 photographs of the eye-region of faces (Figure 2). Participants were asked to choose which of the four words (one target and three foils) described best the complex mental state of the person (for methodological details, see Myers et al. 2003).

Surprised

Sure about something



Joking

Happy

Figure 2. An example for stimuli presented during the Baron-Cohen's Eyes Test

4. Results and discussion

4.1. Experiment 1: Associative Learning in Alcohol Use Disorder

There was no significant difference between AUD patients and controls during the acquisition phase regarding the mean number of errors (controls: 8.9, SD = 2.3; patients: 10.1, SD = 2.6; $t(38) = 1.51$, $P = 0.14$), and the total number of acquisition trials (controls: 35.6, SD = 14.0; patients: 40.2, SD = 16.7, $t(38) = 0.94$, $P = 0.35$).

However, in the transfer phase patients had a selective impairment in the case of new associations ($P < 0.001$) but not in the case of old associations ($P = 0.9$) (Scheffé's post hoc tests).

These results suggest the possibility that basal ganglia related processes are spared, but medial temporal lobe functions remain impaired even after intermediate-term abstinence.

4.2. Experiment 2: “Theory of Mind” in Alcohol Use Disorder

Patients with alcoholism and healthy control subjects displayed nearly identical performances on the Eyes Test. The mean value of the correct answers was 22.4/29 (SD: 3.4) for AUD patients, and 22.5/29 (SD: 2.9) for controls.

This result means using the Eyes Test we could not find ToM deficit in patients with alcoholism, after a longer period of abstinence. This suggests an intact recognition of social emotions and complex mental states in patients with alcoholism after long-term abstinence.

Table 2. Summary of the experiments. Participants, main findings and conclusions

Experiment	Participants	Main findings	Conclusion
I. Associative learning task	- 20 AUD patients (abstinence for > 6 months) -20 Controls	AUD patients show intact performance during the acquisition phase, but impaired performance during the transfer phase.	In AUD patients basal ganglia dependent stimulus and stimulus associative learning was intact, whereas the hippocampus dependent generalization of this knowledge was severely impaired.
II. Eyes task	-30 AUD patients (abstinence for > 6 months) -30 Controls	AUD patients show normal performance in ToM functions.	AUD patients do not demonstrate impairment in decoding of complex social emotions and complex mental states.

Abbreviations in the table: AUD: alcohol use disorder; ToM: theory of mind

5. General discussion

5.1. Discussion of the first experiment

In the first experiment we compared the BG and the hippocampal based learning processes in AUD following longer periods of sobriety. Applying a single task for investigating both functions we conclude that on the BG dependent stimulus associative learning process patients display no significant underperformance, whereas the hippocampus dependent generalization of this knowledge was severely

impaired. These results raise the possibility that basal ganglia related processes are restituted or spared, but medial temporal lobe functions remain impaired even after intermediate-term abstinence.

In accordance with previous research, the present findings support that several months of sobriety is required for cognitive rehabilitation. Fortunately, some cognitive functions do heal faster, but specific cognitive impairments can persist even years.

We should consider the fact that in other studies using similar tasks in different substance use disorders (cocaine, opiate), they found opposite pattern as poor performance on BG dependent and intact performance on MTL dependent activities (Vadhan et al. 2008, Myers et al. 2017).

The BG related functions could be intact in our sample because contrary to the other substance use disorder studies we selected patients with longer sobriety periods, and we tried to select populations free of other influencing factors (other drugs, medications, psychiatric disorders etc.). In more serious alcohol cases, we could expect detectable impairment of associative learning. Also there are data from studies using different methodology (tasks) supporting our results and proposing that alcohol somehow spares this BG dependent function.

Conversely, contrary to other substance use disorder, our AUD patients still exhibited transfer generalization impairments. This suggests that this phase of the associative learning test is highly sensitive for memory impairments in AUD. The special effect of alcohol on the MTL is not a surprise, but it would need further investigation to understand what is the specific pathway causing this difference.

The limitations of our study is the small sample size, the fact that we used only a single test for the assessment of memory, and that we did not examine other, higher executive processes.

5.2. Discussion of the second experiment

In the second experiment we tried to measure the possible social cognitive deficit using an accepted method in AUD population. In contrast to previous expectations, our results in patients with alcoholism after longer periods of abstinence demonstrate no major impairment in decoding of complex social emotions and complex mental states. Our data do not support the conclusion of the recent meta-analysis which emphasizes that social cognition functions are damaged in AUD, and question the hidden assumption that ToM dysfunctions may operate as a diathesis factor patients (Bora and Zorlu 2017; Donadon and Osório 2014; Onuoha et al. 2015).

If we profoundly explore the core data applied in the available meta-analyses, we find that there are limited data available from long-term abstinent patients, and most of these data have not been derived from studies that were planned to investigate the effect of alcohol cessation. However, the main goal of our research was to exclude the acute toxic effect of alcohol.

Then again the major contradiction between our result and some others in the literature could be explained by that our patient population was highly selected. Although we should consider that selecting a suitable group from a scientific perspective, we may exclude the most vulnerable patients, and who need the most support in relapse prevention.

Beside the relative small sample size, the main limitation of the present investigation is that only a single ToM test was applied. Therefore, it is hard to develop a more general conclusion about the social cognitive abilities of patients with alcoholism.

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7. Selected References

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