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How can the depressed mind extract and remember predictive relationships of the environment? Evidence from implicit probabilistic sequence learning

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Running title: Implicit cognition in depression

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Abstract

A growing body of evidence suggests that emotion and cognition are fundamentally intertwined; impairments in explicit, more effortful and attention-dependent cognitive functions have widely been observed in negative mood. Here we aimed to test how negative mood affects implicit cognition that is less susceptible to motivational and attentional factors associated with negative mood. Therefore, we examined implicit learning and retention of predictive relationships in patients with major depressive episode (MDE). Additionally, we directly compared subgroups of patients with major depressive disorder (MDD) vs. bipolar disorder (BD) in order to gain a deeper understanding of how implicit cognition is affected by these conditions. Implicit probabilistic sequence learning was measured by the Alternating Serial Reaction Time Task. The acquired knowledge was retested after a 24-hour delay period. Consistent with the frontostriatal deficits frequently reported in depression, we found weaker learning in patients with MDE, with a more pronounced deficit in patients with MDD compared to BD. After the 24-hour delay, MDE patients (both subgroups) showed forgetting, while the controls retained the previously acquired knowledge. These results cannot be explained by alterations in motivation, attention and reward processing but suggest more profound impairments of implicit learning and retention of predictive relationships among neutral stimuli in depression. To the best of our knowledge, this is the first study investigating retention of implicitly acquired sequential knowledge and reporting deficits in this domain in MDE. Our findings not only contribute to a better understanding of the complex interplay between affect and cognition but can also help improve screening, diagnosis and treatment protocols of depression.

Keywords: depression, fronto-striatal circuits, implicit sequence learning, statistical learning, predictive processing, consolidation

1. Introduction

Contrary to the long-standing view of separated emotional and rational (dual) systems (Figner, Mackinlay, Wilkening, & Weber, 2009; Kahneman, 2011), a growing body of evidence suggests that emotion and cognition are fundamentally intertwined, both on mechanism and on neural level (for a review see Phelps, Lempert, & Sokol-Hessner, 2014). Mood is a relatively lasting affective state that, consequently, can have a persistent effect on cognition. A spate of previous work has found impairments in mood disorders in more effortful and attention-dependent cognitive functions, such as cognitive control, executive functions, planning, explicit/declarative learning and memory (Bora, Harrison, Yücel, & Pantelis, 2013; Bourne et al., 2013; Snyder, 2013). However, it remains unclear to what extent are these impairments due to a general decrease in motivation and/or attentional resources. Here we aimed to test the effect of negative mood on implicit cognition that is less susceptible to motivational and attentional factors in order to gain a deeper understanding of the interplay between affect and cognition. To this end, we examined implicit learning and retention of predictive relationships in patients with Major Depressive Episode (MDE).

MDE is one of the most common psychiatric diagnoses (Patten, 2009) characterized by persistently low level of mood that affects interest in daily activities, energy level, sleep, psychomotor functioning (APA, 2000), and more broadly, social and occupational functioning (Godard, Grondin, Baruch, & Lafleur, 2011). Depending on the alterations between different mood states, MDEs can occur in patients with Unipolar Major Depressive Disorder (MDD), where negative mood states can alternate with euthymic phases, and in patients with Bipolar Disorder (BD), where negative mood states alternate with manic or hypomanic phases (APA, 2000). Alterations in the neural circuitries involved both in emotion regulation and cognition have been shown in MDE, primarily in the fronto-striatal network (Bora, Harrison, Davey, Yücel, & Pantelis, 2012; Brambilla et al., 2001; Koolschijn et al., 2009). Some studies have

reported larger morphometric and functional abnormalities of the striatum in patients with MDD compared to BD, where it was mainly present in association with the length of illness (Brambilla et al., 2001; Savitz & Drevets, 2009). Given the striatum's prominent role in predicting future outcomes based on previous experience (Balleine, Delgado, & Hikosaka, 2007; den Ouden, Daunizeau, Roiser, Friston, & Stephan, 2010; Li & Daw, 2011), one could assume that implicit learning of predictive relationships is affected in MDE.

Implicit learning occurs when predictive relationships in form of statistical regularities or sequence of events are extracted from the environment without putting conscious effort into the process or realizing the learning process at all (A. S. Reber, 1993). Research has showed that implicit learning plays a critical role in guiding our behavior in many day-to-day activities (Kaufman et al., 2010; Norman & Price, 2012; Romano Bergstrom, Howard, & Howard, 2012) and it primarily relies on the fronto-striatal circuitries (Doyon et al., 2009; Hikosaka et al., 1999; Poldrack et al., 2005; P. J. Reber, 2013). The most common task for measuring implicit learning is the Serial Reaction Time (SRT) Task (Nissen & Bullemer, 1987), in which participants respond to repeating sequences of stimuli presented on the computer screen. With practice, participants become faster in responding to the repeating sequences, and they slow down when the sequence pattern is removed at the end of practice (random block). Studies with SRT found impaired learning during a depressive episode in MDD (Exner, Lange, & Irle, 2009; Naismith, Hickie, Ward, Scott, & Little, 2006) as well as in BD (Chrobak et al., 2015). However, these studies had a limited capacity to disentangle sequence-specific learning from more general psychomotor impairments: if patients do not show RT improvement during the sequence blocks at all, then no RT rebound can be expected on the random block (Borbély-Ipkovich, Janacsek, Németh, & Gonda, 2014; Klivenyi et al., 2012). Hence, based on these studies, one cannot conclude whether implicit learning of sequences is impaired or intact in depression. Moreover, SRT tasks have several additional

drawbacks: participants easily become aware of the sequence structure and explicit, attention-dependent strategies may influence their performance (Perruchet, Bigand, & Benoit-Gonin, 1997), and usually a short version of the task is administered (20-30 sequence presentations), making it difficult to distinguish between a total inability to learn the sequences or just a partial impairment (e.g., a slower pace of learning).

Here we used the Alternating Serial Reaction Time (ASRT) task (J. H. Howard, Jr. & Howard, 1997) as a more suitable tool for measuring implicit learning of predictive relationships. In this task, random elements are inserted in the repeating pattern, creating an eight-element probabilistic sequence (e.g., 2r3r1r4r, where numbers indicate locations on the screen, and r indicates a randomly chosen location). Stimulus n can be predicted based on the stimulus $n-2$ (e.g., 2_3, where _ indicates any location out of the four possible ones) but only with a 62.5% certainty because other stimulus-triplets can also be formed due to the random elements (e.g., 2_1, 2_4, 2_2) in 37.5% of the time. The former, more predictable stimuli are referred to as high-predictability triplets and the latter ones as low-predictability triplets. Because of these triplet characteristics, the task is also often referred to as an associative learning (Barnes, Howard, Howard, Kenealy, & Vaidya, 2010) or statistical learning task (Nemeth, Janacsek, & Fiser, 2013). Learning is defined as RT difference in responses to high- vs. low-predictability triplets, which can be measured from the very beginning of the task. The ASRT task is considered a purer measure of implicit learning, since participants remain unaware of the stimulus structure even after extended practice (i.e., ten days; D. V. Howard, Howard, Japikse, DiYanni, et al., 2004), and is appropriate to measure the time course of learning, as a typical learning session includes at least 200 sequence presentations (D. V. Howard, Howard, Japikse, DiYanni, et al., 2004; J. H. Howard, Jr. & Howard, 1997; Nemeth, Janacsek, & Fiser, 2013).

The goal of our study was threefold. First, we aimed to explore implicit probabilistic sequence learning in patients with MDE using a task that overcomes several drawbacks of previous research. Here we used the ASRT task that remains implicit for the participants, and enables us to continuously measure learning performance from the very beginning of the task through a longer learning session (200 sequence presentations). Second, we aimed to characterize the time course of implicit sequence learning not only during the learning phase, but also after a 24-hour delay period, which is an entirely novel contribution to the field as, to the best of our knowledge, no study has yet investigated the retention of implicitly acquired sequential knowledge in MDE. Thus, we tested whether participants were able to retain the acquired sequence knowledge for a relatively longer stretch of time after the initial acquisition. Third, although our primary aim was to examine implicit learning and retention in patients with MDE compared to the healthy controls, we also planned to directly compare – for the first time – the implicit learning and retention performance of MDD vs. BD patients. We hypothesized weaker learning and retention performance in patients with MDE compared to the controls. Based on the fronto-striatal dependency of implicit sequence learning and retention, larger impairments were expected in MDD compared to BD.

2. Materials and methods

2.1 Participants

Twenty patients with MDE ($M_{\text{age}} = 45.95$, $SD_{\text{age}} = 12.39$; $M_{\text{education}} = 14.20$, $SD_{\text{education}} = 3.16$; 13 females) were recruited from Kutvolgyi Clinical Center at Semmelweis University in Budapest, Hungary. They had been diagnosed by a team including a licensed clinical psychologist and a board-certified psychiatrist at the clinical center. Based on DSM-IV-TR (APA, 2000), ten patients met the criteria for a diagnosis of MDD, and the other ten patients met the criteria for a diagnosis of BD (demographics by subgroup are presented in Table 1).

Exclusionary criteria included co-morbid schizophrenia, ADHD, current anxiety disorder, current substance use disorder, and any neurological disorder (Burdick, Ketter, Goldberg, & Calabrese, 2015). All patients received medication at the time of the study (details are reported in Table 1).

Twenty-one healthy control participants were matched to patients based on age, gender and years of education (Table 1). Exclusionary criteria included a current or lifetime diagnosis of any psychiatric or neurological disorder. In addition, Beck Depression Inventory (BDI; Beck, Steer, & Brown, 1996) was administered for screening subclinical depression in the controls. Based on their high BDI score, two participants were excluded from the analyses. Thus, the final sample consisted of 19 healthy individuals. Participation in the study was voluntary, with no incentives offered. All participants signed an informed consent. Ethical permission was obtained from the institutional ethical committee of Semmelweis University.

Table 1. Demographic and clinical data (means, standard deviations, and proportions) for the control (n = 19) and patient groups (n = 20, 10 diagnosed with MDD, and 10 diagnosed with BD). The current state of anxiety (State-Trait Anxiety Inventory – STAI), mood (Positive and Negative Affective Schedule – PANAS), and depressive symptoms of the participants were evaluated (Beck Depression Inventory – BDI).

	Control	MDD	BD	<i>p</i>-value
Age (years)	44.58 (16.25)	47.90 (10.77)	44.00 (14.13)	.801
Education (years)	14.32 (3.28)	13.20 (3.58)	15.20 (2.44)	.379
Gender (F/M)	12/7	6/4	7/3	.891
BDI	4.63 (4.64)*	33.70 (8.68)	26.40 (10.74)	< .001
STAI-S	39.47 (8.69)*	52.40 (9.88)	52.90 (9.86)	< .001
PANAS-Positive affect	39.68 (4.61)*	27.40 (9.30)	23.60 (7.56)	< .001
PANAS-Negative affect	14.11 (4.34)*	24.30 (8.99)	24.70 (11.02)	.003
Medications: AD/AP/AE/BD/L	-	9/5/5/3/1	10/10/5/2/1	.010 (AP only)

Notes: P-values of univariate ANOVAs (for comparisons of three groups), and chi-squared tests (for comparisons of gender and medication proportions across groups) are reported. The patient groups had similar BDI, STAI-S, and PANAS scores but differed significantly from the controls (marked with an asterisk, *, based on LSD post hoc tests). As it is typical in the clinical profile of MDE, 10/10 in the BD group took antipsychotic medications compared to the 5/10 patients in the MDD group. Abbreviations of the medication categories: AD – antidepressants, AP – antipsychotics, AE – antiepileptics, BD – benzodiazepines, L – lithium.

2.2 Task and procedure

Implicit probabilistic sequence learning was measured by the ASRT task (J. H. Howard, Jr. & Howard, 1997; Nemeth, Janacsek, Londe, et al., 2010). In this task, a target stimulus appeared in one of four possible locations on the screen, in a horizontal arrangement. Participants were asked to press the corresponding key (Z, C, B and M) as quickly and accurately as they could. Importantly, the stimulus remained on the screen until participants pressed the correct button, which served as the minimum (and sufficient) attentional requirement to perform the task. This has been proven enough to exhibit significant learning, as healthy participants could show learning in this task even when their deliberate attention was directed to an effortful secondary task that they performed simultaneously (Nemeth et al., 2011).

The appearance of stimuli followed a predetermined order, which was unknown for them. Stimuli were presented in blocks of 85 trials. The first five trials were randomly selected (practice purposes only), then an eight-element alternating sequence was repeated ten times (e.g., 2r3r1r4r, where 1–4 indicate the target locations, and r indicates a randomly selected position out of the four possible ones). This structure results in some of the three consecutive trials (*triplets*) occurring more frequently than others. Accordingly, each item was categorized as the third element of either a high- or low-predictability triplet. With practice, people respond more quickly to the high- compared to the low-predictability triplets, revealing probabilistic sequence (or statistical) learning.

The ASRT task was administered in two sessions. It consisted of 20 blocks in the Learning Phase, and of 5 blocks in the Retention Phase. The delay between the two sessions was 24 hours. Explicit knowledge of the participants about the sequential structure was tested by a questionnaire at the end of the Retention Phase (Nemeth, Janacsek, Londe, et al., 2010; Song, Howard, & Howard, 2007). None of the participants reported noticing the sequence in the task. This observation is in line with previous studies showing that participants remain unaware of the sequence even after extended practice, or when more sensitive recognition tests are used to assess explicit knowledge (D. V. Howard, Howard, Japikse, DiYanni, et al., 2004; Song et al., 2007).

2.3 Statistical analysis

Statistical analysis was based on previous studies (Nemeth, Janacsek, Londe, et al., 2010; Romano Bergstrom et al., 2012); epochs of five blocks were analyzed instead of single blocks. The Learning Phase consisted of four epochs, while the Retention Phase consisted of one epoch. Similarly to previous ASRT studies that observed ceiling effects in accuracy, we focused on RTs (accuracy results are presented in Supplementary materials). We calculated median RTs for correct responses only for each participant and each epoch, separately for high- and low-predictability triplets. We also calculated learning scores as a difference between RTs for low- vs. high-predictability triplets. Larger scores indicate better learning performance.

Learning and retention was analyzed in mixed design analyses of variance (ANOVAs). As patients with MDE typically respond with slower RTs (Bora et al., 2013; Mora, Portella, Forcada, Vieta, & Mur, 2013), we conducted additional ANOVAs on normalized RTs (calculated as median RTs for each triplet type and each epoch divided by the median RT of Epoch 1). For the sake of brevity, we report the results of these ANOVAs only

for the comparisons relevant for the conclusions. Additionally, we determined for each participant whether they exhibited learning (learning score is above zero) or not (learning score is below zero) in a given epoch. The number of participants who showed above or below zero performance was compared across groups using chi-squared tests. Finally, we also conducted a Pearson's correlation analysis to explore the relationship between mood (measured by PANAS scores) and learning performance (focusing on the learning scores of Epoch 4 and 5).

Beyond the main goal of characterizing implicit probabilistic sequence learning and retention in patients with MDE, we also compare performance of the MDD and BD subgroups to that of the controls. Although the sample size of these patient subgroups is relatively small (see Supplementary materials for statistical power calculations), we believe that these analyses can give us important insights into whether learning and retention is differently affected in these clinical conditions and can formulate further research questions to be tested in future studies.

3. Results

3.1 Do patients with MDE learn the sequential regularities in the Learning Phase?

Implicit learning in Session 1 was analyzed by a mixed design ANOVA with TRIPLET (2: high vs. low) and EPOCH (1–4) as within-subjects factors and GROUP (control vs. patients with MDE) as a between-subjects factor. Overall, patients responded with significantly slower RTs compared to the controls (main effect of GROUP: $F(1, 37) = 12.231, \eta_p^2 = 0.248, p = .001$). Irrespectively of triplet type, RTs significantly decreased over epochs (main effect of EPOCH: $F(3, 111) = 8.743, \eta_p^2 = 0.191, p = .001$), indicating general skill improvements due to practice (Figure 1AB). The time course of this general speed-up was similar in the control and patient groups (EPOCH*GROUP interaction: $F(3, 111) = 0.310, \eta_p^2 = 0.008, p = .678$).

Participants showed significant sequence learning, such that they responded faster to high-predictability triplets compared to the low-predictability ones (main effect of TRIPLET: $F(1, 37) = 14.908$, $\eta_p^2 = 0.287$, $p < .001$). Interestingly, the degree of sequence learning was different between the two groups (TRIPLET*GROUP interaction: $F(1, 37) = 5.238$, $\eta_p^2 = 0.124$, $p = .028$): while the controls showed significant learning ($M_{\text{Low-High}} = 10.316$ ms, $p < .001$), the patients did not ($M_{\text{Low-High}} = 2.638$ ms, $p = .267$). These results remained stable even after controlling for between-group overall RT differences (TRIPLET*GROUP interaction on normalized RTs: $p = .007$; controls' learning: $p < .001$; patients' learning: $p = .188$).

A more fine-grained inspection of the learning scores revealed that the controls demonstrated significant learning in Epoch 2–4 ($ps < .032$). In contrast, the patients' learning score did not differ significantly from zero in Epoch 1–3 ($ps > .683$) but was significant in Epoch 4 ($p = .003$). The learning score in Epoch 4 was similar in the control and patient groups ($p = .902$). Possibly due to the pattern of the controls showing significant learning in three out of four epochs, whereas the patients showing no learning in the same number of epochs, the TRIPLET*EPOCH and TRIPLET*EPOCH*GROUP interactions failed to reach significance ($ps > .282$). Nevertheless, the epoch-by-epoch inspection revealed important information: although the patients, overall, showed no significant learning in the Learning Phase, they might still be able to pick up sequential regularities but in a slower pace (indicated by the significant learning score in Epoch 4).

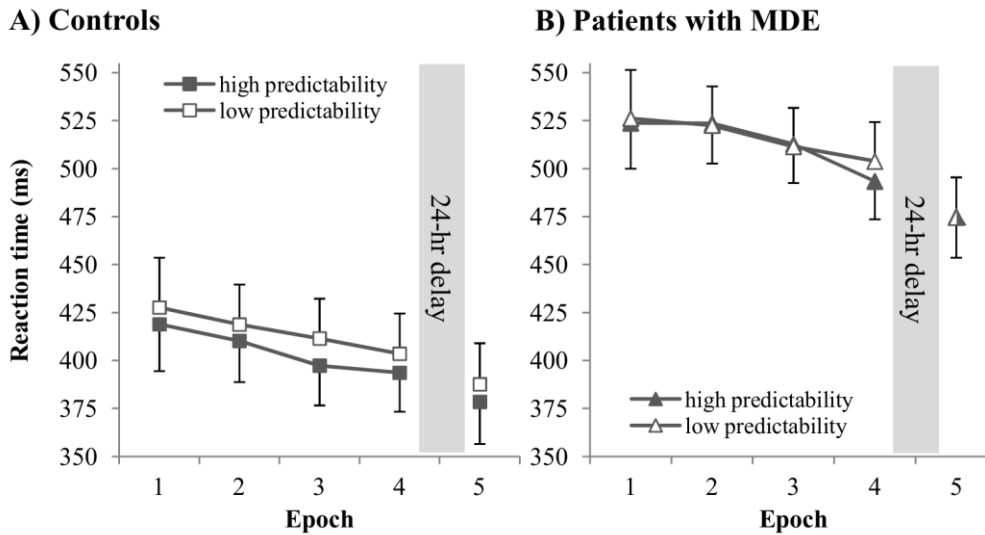


Figure 1. Reaction times (RTs) across the Learning Phase (Epoch 1–4) and Retention Phase (Epoch 5) for the controls (A) and the patients with MDE (B). Overall, patients had slower RTs. Both groups showed speed-up due to practice, exhibiting general skill improvements. The control group responded faster to the high-predictability triplets compared to the low-predictability ones, revealing significant sequence learning. Patients with MDE responded similarly to high- and low-predictability triplets (except for Epoch 4), indicating weaker (nonsignificant) sequence learning. There was a general speed-up from Epoch 4 to 5, to a similar extent in both groups, indicating offline general skill improvements. Error bars represent Standard Error of Mean (SEM).

3.1.1 Do the MDD and BD group show different performance in the Learning Phase?

We tested potential group differences between the patient subgroups by conducting a similar ANOVA as described above with SUBGROUP (control vs. MDD vs. BD) as a between-subjects factor. The ANOVA further confirmed group differences in sequence learning (TRIPLET*SUBGROUP interaction: $F(2, 36) = 5.275$, $\eta_p^2 = 0.227$, $p = .010$). While the BD group showed significant learning ($M_{\text{Low-High}} = 7.513$ ms, $p = .023$), the MDD group did not ($M_{\text{Low-High}} = -2.237$ ms, $p = .483$), suggesting that the control vs. patient group differences observed above are primarily led by the MDD group's weaker performance. These results remained stable even after controlling for between-group overall RT differences (TRIPLET*GROUP interaction on normalized RTs: $p = .004$; learning_{Controls}: $p < .001$,

learning_{BD}: $p = .022$, learning_{MDD}: $p = .677$). The LSD post hoc test revealed that the MDD group's learning score was significantly different from that of the BD and control groups ($p = .035$, $p = .003$; respectively), while the latter two groups' scores did not differ significantly ($p = .477$). Other interactions involving the SUBGROUP factor did not reach significance ($ps > .184$). The more fine-grained inspection of the learning scores in the patient subgroups further supported the main findings of the MDE vs. control comparison, showing that the overall slower pace of learning finally yielded learning scores similar to that of the controls by the end of the Learning Phase (Epoch 4: $ps > .498$), although the MDD group's learning score was above zero only on a trend level ($p = .086$), while the BD group's learning score was significantly greater than zero ($p = .010$).

3.2 Do patients with MDE retain the acquired knowledge over the 24-hr offline period?

Offline changes over the 24-hr delay were analyzed by comparing RTs from the last epoch of the Learning Phase and the one epoch of the Retention Phase. These variables were submitted to a mixed design ANOVA with TRIPLET (2: high- vs. low-predictability) and EPOCH (2: Epoch 4 vs. 5) as within-subjects factors, and GROUP (control vs. patient) as a between-subjects factor.

Patients showed overall slower RTs compared to the controls (main effect of GROUP: $F(1, 37) = 10.912$, $\eta_p^2 = 0.228$, $p = .002$). As expected, RTs significantly decreased during the 24-hr period (main effect of EPOCH: $F(1, 37) = 15.759$, $\eta_p^2 = 0.299$, $p < .001$), such that participants responded faster in the Retention Phase compared to the end of the Learning Phase, indicating offline general skill improvements (Figure 1AB). The degree of offline improvement was similar in the groups (EPOCH*GROUP interaction: $F(1, 37) = 0.700$, $\eta_p^2 = 0.019$, $p = .408$).

The main effect of TRIPLET was significant ($F(1, 37) = 14.958, \eta_p^2 = 0.288, p < .001$), indicating sequential knowledge with faster responses on high- than on low-predictability triplets in these epochs across groups (TRIPLET*GROUP interaction: ($F(1, 37) = 1.406, \eta_p^2 = 0.037, p = .243$). Interestingly, there was a decrease in sequential knowledge over the offline period on a trend level (TRIPLET*EPOCH interaction: $F(1, 37) = 2.589, \eta_p^2 = 0.065, p = .110$). This decrease was significant in the patient group only ($M_{\text{Epoch 4}} = 10.775$ vs. $M_{\text{Epoch 5}} = -0.325$ ms, $p = .036$), while knowledge was retained in the control group ($M_{\text{Epoch 4}} = 9.868$ vs. $M_{\text{Epoch 5}} = 9.211$ ms, $p = .898$). The TRIPLET*EPOCH*GROUP interaction, however, failed to reach significance ($F(1, 37) = 2.028, \eta_p^2 = 0.052, p = .163$). The ANOVA on normalized RTs yielded similar results (offline change_{controls}: $p = .923$, offline change_{patients}: $p = .060$; TRIPLET*EPOCH*GROUP interaction $p = .173$).

Additionally, we compared the number of participants in each group who showed above zero learning performance, separately for Epoch 4 and 5. In Epoch 4, 17 out of the 19 controls and 16 out of the 20 patients showed above zero performance ($\chi^2(1) = .672, p = .412$). In contrast, in Epoch 5, 15/19 controls but only 9/20 patients exhibited above zero performance, leading to significant group differences ($\chi^2(1) = 4.744, p = .029$). This analysis provides further support for and extends the results of the ANOVA: it suggests weaker retention of the sequential knowledge in the patient group compared to the controls.

3.2.1 Do the MDD and BD group show different performance over the 24-hr offline period?

We conducted a mixed design ANOVA similar to the one described above with SUBGROUP (control vs. MDD vs. BD) as a between-subjects factor. In this ANOVA, interactions involving the SUBGROUP factor did not reach significance ($ps > .354$). The MDD and BD groups showed similar performance, with a decrease in sequential knowledge over the offline

period in both patient groups (MDD: $M_{\text{Epoch 4}} = 8.200$ vs. $M_{\text{Epoch 5}} = -0.600$ ms; BD: $M_{\text{Epoch 4}} = 12.700$ vs. $M_{\text{Epoch 5}} = -0.050$ ms). The ANOVA on normalized RTs yielded similar results (interactions with SUBGROUP: $ps > .364$). The additional analysis comparing the number of participants who showed above zero statistical learning performance in the three groups. We found no significant group differences in Epoch 4: 9/10 MDD and 7/10 BD patients showed above zero performance compared to 17/19 controls ($\chi^2(2) = 2.208, p = .332$). In Epoch 5, there was a trend for group differences ($\chi^2(2) = 4.955, p = .084$): only 5/10 MDD and 4/10 BD patients showed above zero performance compared to 15/19 controls. These findings are in line with the ANOVA results, suggesting a similar pattern of offline changes in MDD and BD.

3.3 Is the current state of mood related to statistical learning performance?

First, we examined the relationship between Positive- and Negative-scales of PANAS and learning score of Epoch 4, separately for the controls and for the patients with MDE (Figure 2). This appeared to be the best approach to characterize learning performance since by the end of the Learning Phase all groups achieved similar learning performance, thus, learning scores of previous epochs or an overall learning score would have underestimated learning performance in patients. We found significant, moderate correlation between learning score of Epoch 4 and PANAS-Positive ($r = .458, p = .043$) as well as PANAS-Negative scales ($r = -.450, p = .047$) in the patient group, both pointing to the same direction: more positive (and less negative) mood was associated with better sequence learning performance. This result was not related to overall speed differences among participants: overall RTs were not correlated either with the learning score or with the PANAS scores ($rs < -.167, ps > .481$). We found no relationship between current mood state and learning performance in the controls (Learning score in Epoch 4 with PANAS-Positive: $r = -.199, p = .413$, with PANAS-

Negative $r = .087$, $p = .724$). Importantly, this analysis was conducted separately for controls and for patients with MDE but not separately for patient subgroups, as they did not differ on PANAS scores (see Table 1). Nevertheless, Figure 2 shows data of patients with MDD and BD in different markers, and suggests a similar relationship between mood and learning in both subgroups.

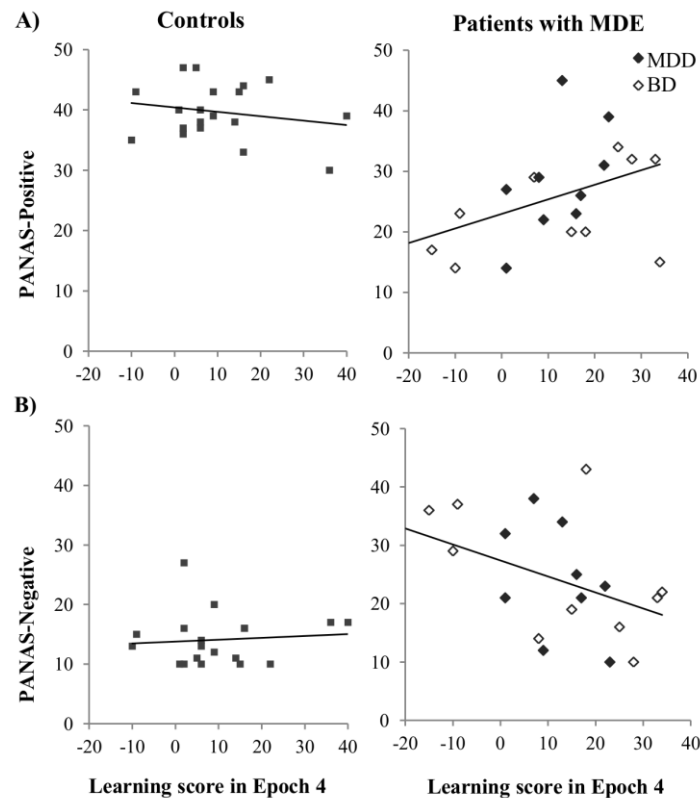


Figure 2. Relationship between the sequence learning score of Epoch 4 and PANAS-Positive scale (A) and PANAS-Negative scale (B) for the control and patient groups (left and right panels, respectively). Data of patients with MDD and BD are shown in different markers. Sequence learning positively correlated with PANAS-Positive and negatively correlated with PANAS-Negative scales in the patient group, while there was no significant correlation between these variables in the control group.

We conducted a similar correlation analysis for the learning score of Epoch 5 to explore the relationship between affect and learning performance after the 24-hour delay period. We found no significant associations either in the control or in the patient groups ($r_s < -.233$, $p_s > .324$).

4. Discussion

Compared to the large body of research exploring the impairments of explicit, attention-dependent cognitive functions in MDE, characterization of implicit cognition has hardly been studied in this population. Here we aimed to examine implicit probabilistic sequence learning and retention in patients with MDE. To the best of our knowledge, this is the first study that investigates not only implicit learning but also retention in depression. Additionally, we compared subgroups of patients with MDD vs. BD in order to gain a better understanding of how these conditions affect implicit cognition. Such direct comparison of patients with MDD and BD in this cognitive domain was also missing in previous research. We found weaker implicit learning in patients with MDE, with a more prominent deficit in MDD compared to BD. These findings remained stable even after controlling for the between-group RT differences. After the 24-hour delay, patients with MDE (both subgroups) showed forgetting, while the controls retained the previously acquired knowledge.

Our results of weaker implicit sequence learning in patients with MDE are in line with previous research (Chrobak et al., 2015; Exner et al., 2009; Naismith et al., 2006; Naismith et al., 2010). Nevertheless, these studies provided only limited evidence for disentangling sequence-specific learning from more general psychomotor impairments. For example, the BD patients in Chrobak et al.'s (2015) study did not show speed-up during the sequence blocks at all that could be caused either by a deficit in general skill learning and/or in sequence-specific learning (Borbély-Ipkovich et al., 2014; Klivenyi et al., 2012). While Exner et al. (2009) report some general speed-up besides the deficit in sequence learning in the MDD patients, the Naismith et al. studies did not report data in that regard (Naismith et al., 2006; Naismith et al., 2010). Here we were able to disentangle general speed-up from learning the sequential regularities, and we showed that patients with MDE exhibit general skill

improvements comparable to those of the controls, while they have difficulties learning the sequential/statistical regularities. Our study thus provides direct evidence for weaker implicit sequence learning in patients with MDE.

Previous studies did not directly compare implicit cognition in MDD vs. BD (Chrobak et al., 2015; Exner et al., 2009; Naismith et al., 2006; Naismith et al., 2010). Although we had a relatively small sample size in the MDD and BD subgroups, the statistical power analysis (see Supplementary materials) showed that this sample size is sufficient to detect learning in these subgroups. Our results suggest that MDD patients' implicit learning capacity may be more affected than that of the BD patients, which is consistent with the neuroimaging studies showing greater alterations of the striatum in MDD compared to BD (Brambilla et al., 2001; Savitz & Drevets, 2009). A dissociation might be present between explicit, attention-demanding vs. implicit, attention-independent processes in depression, as BD patients has been previously shown to have larger deficits in the explicit domain compared to MDD patients (Gildengers et al., 2012; Maalouf et al., 2010; Smith, Muir, & Blackwood, 2006), while opposite pattern might exist in the implicit domain. Future studies should elaborate this potential dissociation, as well as directly contrast neural correlates of implicit learning in MDD vs. BD to gain a deeper understanding of this behavioral pattern.

The more fine-grained analysis of the Learning Phase revealed a slower pace of learning in patients with MDE, in that they did not show significant learning until the very last part of the Learning Phase. Interestingly, however, patients with MDE (both subgroups) and the controls showed comparable learning performance in Epoch 4. This finding indicates that the integrity of the neural networks underlying implicit learning is at least partly preserved in these patients. It is important to note, that implicit learning is generally less susceptible to illness compared to the more explicit functions (e.g., executive functions, attention, working memory, declarative learning). Using the exact same task as in the current study, implicit

learning was found to be preserved in many patient populations, including autism (Nemeth, Janacsek, Balogh, et al., 2010), obstructive sleep apnea (Nemeth, Csábi, Janacsek, Varszegi, & Mari, 2012), patients with sleep-disordered breathing (Csábi, Benedek, Janacsek, Katona, & Nemeth, 2013), and alcohol-dependent patients (Virag et al., 2015). So far, weaker learning has only been observed in schizophrenia (Schwartz, Howard, Howard, & Hovaguimian, 2003) and in Mild Cognitive Impairment (Nemeth, Janacsek, Király, et al., 2013). Thus, finding weaker learning performance in this task is the exception rather than the rule. Interestingly, some studies have argued that depression and Mild Cognitive Impairment have a common disorder pathway (Panza et al., 2010; Zihl, Reppermund, Thum, & Unger, 2010), and similarly, research has found quantitatively but not qualitatively different neurocognitive profile in schizophrenia and in bipolar disorder (Balanzá-Martínez et al., 2005; Vöhringer et al., 2013). Our results are in line with and extend these arguments, showing weaker implicit learning/retention performance in patients with MDD and BD.

Retention of the acquired knowledge was tested after a 24-hour delay. To the best of our knowledge, no study has yet investigated retention of the implicitly acquired sequential knowledge in patients with MDE. As it is typical in this domain (Nemeth, Janacsek, Londe, et al., 2010; Song et al., 2007), we found retention of the acquired sequential knowledge in the controls. In contrast, patients exhibited weaker performance after the delay compared to the end of learning. Further analysis revealed that a similar number of MDD and BP patients showed weaker retention, suggesting that the mechanisms involved in the consolidation/retention of sequential knowledge are equally affected in these conditions.

We also found that implicit learning performance was related to the current state of mood measured by PANAS in the patients with MDE. Better learning was associated with less negative (and more positive) mood, confirming that mood indeed has an impact on implicit learning of predictive relationships. It is unlikely that this finding is due to general

motivational or attentional effects associated with negative mood as implicit learning is less susceptible to these effects, and significant learning can occur even when participants' deliberate attention is directed to another, effortful, simultaneously executed task (Nemeth et al., 2011) (see also Task and Procedure). Moreover, we examined learning of predictive relationships between neutral stimuli with no rewards given, that allowed to control for alterations in reward processing and in responses to emotional stimuli often observed in depression (Heller et al., 2009; Levy-Gigi & Kéri, 2015; Pizzagalli et al., 2009). The current study thus shows impairments in implicit learning of predictive relationships between neutral stimuli without rewards in depression. In healthy participants previous findings on mood effects are mixed: in one case negative mood induction led to weaker learning (Shang, Fu, Dienes, Shao, & Fu, 2013), whereas the other study failed to find a negative mood effect on implicit sequence learning (Pretz, Totz, & Kaufman, 2010). Positive mood induction did not influence learning in either cases (Pretz et al., 2010; Shang et al., 2013). Importantly, participants' mood was experimentally altered in both studies, in contrast to our study where the control participants had a neutral (or slightly more positive) mood. Our findings are consistent with these previous studies and suggest that greater shift away from the neutral mood (and towards the negative extremes) has an adverse effect on implicit sequence learning.

Dysfunction of the HPA axis is a typical accompaniment of affective disorders (Villanueva, 2013). The dysregulation of the stress hormones have been observed in depression, including increased excretion and increased levels of cortisol, and increased response to psychological stressors (Anacker et al., 2013). We are aware of one study that directly tested the effect of cortisol on implicit sequence learning and found that cortisol administered orally to healthy adults impaired learning (Römer, Schulz, Richter, Lass-

Hennemann, & Schächinger, 2011). Consequently, cortisol alterations in depression can contribute to the weaker learning and retention performance observed in the current study.

Our study has some limitations. We used only a short questionnaire (Nemeth et al., 2012; Song et al., 2007) to assess whether participants became aware of the ASRT sequence. Importantly, we decided to use the ASRT task because it is well documented that participants do not become aware of the underlying sequence/statistical structure embedded in the task even after extended practice (e.g., ten days; D. V. Howard, Howard, Japikse, DiYani, et al., 2004) and when examined with more sensitive recognition and generation tests (Kóbor, Janacsek, Takács, & Nemeth, 2017; Song et al., 2007), thus it indeed measures *implicit* learning. Nevertheless, it is preferable to include more sensitive measures of awareness in future studies to complement the results of the short questionnaire. It is also important to note that we had a relatively small sample size in the MDD and BD subgroups that may have hindered our ability to detect significant group differences in some cases. For instance, the pattern of group differences in learning was similar between the RT and accuracy data but the latter one failed to reach significance (see Supplementary materials), presumably due to the typical ceiling effects observed in accuracy and the limited statistical power associated with the small sample sizes. In addition, in the case of the 24-hour delay, MDE patients (both subgroups) showed declined RT learning scores compared to the controls who retained the acquired knowledge over the delay period but the group comparisons did not reach significance. These results might be partly explained by the larger within-group heterogeneity among MDE patients that was shown by the additional analyses and call for further studies with larger sample sizes to replicate the current findings and extend towards a more comprehensive characterization of between- and within-group differences.

In conclusion, we showed weaker implicit probabilistic sequence learning in patients with MDE, with more negative mood related to greater impairment in learning. These

findings cannot be explained by general motivational and/or attentional alterations associated with negative mood but indicate a more fundamental deficit of learning predictive relationships in depression. Patients with MDD seemed to have larger impairments compared to patients with BD, suggesting a potential dissociation between the implicit and explicit cognition in these clinical conditions that should be further investigated in future studies. After the 24-hour delay, patients with MDE (both subgroups) showed a decreased performance, indicating that not only implicit learning is affected by depression but the retention of the acquired knowledge as well. Our findings can contribute to a better understanding of the complex interplay between affective states and cognition, and suggest that the consequences of negative mood on implicit cognition should be more closely monitored in patients with MDE and potentially included in the assessment of the effectiveness of various treatment protocols.

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Authors' contribution

The experimental design was developed by DN, KJ and XG. XG was part of the clinical team administering the diagnosis of the patients. Data was collected by EBI and XG, and analyzed by KJ and EBI. The manuscript was written by KJ, ND, XG and EBI.

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The authors report no conflict of interest.

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