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Does Reinfection Exacerbate Cognitive Impairment? The Relationship between Covid-19 and Occasion Setting

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ABSTRACT

It has been shown that covid can negatively affect an individual's cognitive functioning. This study used the conditional discrimination paradigm, which aims to explore the relationships between the number of covid infections and aspects of an individual's cognitive functioning. Sixty-six participants completed an online survey of their covid history, as well as one biconditional discrimination task and a simple associative task. Compared to the simple associative task, the biconditional discrimination task requires participants to establish a stimulus-stimulus association through task-setting cues, which are regarded as the occasion setter. Importantly, it needs more complex process in the biconditional discrimination task, such as executive function, whereas simple associative task does not need this ability. ANOVA results showed that the number of infections did not influence task performance, but regression indicated a relationship between these two. In the biconditional discrimination task, the number of infections varies in relation to the performance of the task. However, in the simple associative task, there is no difference between the number of infections and the performance. The relationship between reinfection and cognitive impairment needs to be further explored in the future.

KEYWORDS

Covid-19; Reinfection; Cognitive Function; Associative Learning.

1. INTRODUCTION

It has been shown that covid-19 negatively impacts individuals' cognitive function. For example, a systematic review [1] noted impaired executive function, attention, and memory from the acute phase even to seven months after being infected in patients with no history of cognitive impairment prior to infection. There are also asymptomatic patients, and one study investigating this population using MoCA found that although there were no significant differences in overall cognitive scores between the asymptomatic and healthy groups, impairments in specific aspects such as visuoperception and fluency were observed [2]. Therefore, differentiating the severity of symptoms is also crucial in cognitive testing patients with a history of covid-19 infection. However, it cannot be overlooked that the assessment tasks used in these studies varied, with the majority using the MoCA, but one study[3] noted that this approach might be difficult to detect minor aspects of cognitive change.

It has also been observed that cognitive impairment in patients infected with covid-19 is related to several factors, such as medication, age, and inflammation due to fever. It was found that the severity of persistent symptoms at the time of infection was associated with deficits in cognitive function[4]. Specifically, the more severe the persistent symptoms, the more likely the patient was to make errors on the Word List Recognition Memory Test, Category Fluency Test, and Pictorial Associative Memory Test.

Unfortunately, people who have been infected once are still at risk of being infected a second time or even more times. A systematic review stated that the time between first infection and reinfection could be as short as 19 days [5]. Especially in immunocompromised individuals or those who have developed fewer antibodies over time, the chances of reinfection will increase [6]. In addition, the constant variation of the covid-19 is vital to be considered. Although reinfected patients did not present with severe symptoms, it was possible to identify a significant proportion of individuals who had been infected with covid as being reinfected with the newly emerged variant[7]. Cognitive impairment due to covid-19 may be long-term and require more time to recover and treat. If reinfection occurs during a period of incomplete recovery, it may make the individual's impairment more severe.

Vaccination is also an aspect worth considering. As the number of variants of covid-19 has increased, so has the number of people vaccinated, and the risk of post-infection sequelae appears to be lower in those who have been vaccinated. In some of the early studies of covid-19, most patients had no history of vaccination, and later studies have rarely included a discussion of the relationship between vaccination status and cognitive ability, so this factor also appears to be necessary.

In order to understand the impact of covid-19 on the cognitive function of individuals, research should be more diverse, using different methods of measuring individual cognition, as well as adding more factors to refine this area in order to provide more comprehensive aid to the treatment of infected individuals in the future. In this study, a task related to executive function was used.

There is a relationship between cued task solving as well as associative learning and cognitive function. In a simple associative task, there is a specific response to a specific stimulus. Specifically, participants could learn that an X response is required in the presence of stimulus A and a Y response is required in the presence of stimulus B[8]. However, some other tasks cannot be explained by simple associative learning. In the training of conditioned responses in animals, when a conditioned stimulus(CS) is trained to indicate an unconditioned stimulus(US), its conditioned response is restricted if it is conditioned by a stimulus known as the occasion setter[9]. Specifically, when the occasion setter(A) is presented before conditioned stimulus(X), the animal will respond more to the unconditioned stimulus than when X is presented alone.

The discrimination task has been used in several studies. For example, one research found that the ability of mice to engage in goal-directed behaviour through task-setting cues was impaired after briefly breaking dopamine function[10]. Additionally, when the medial prefrontal cortex (mPFC) is lesioned in mice, this affects the formation of the association between the OS to the CS and the US, and it follows that the regulation of this association is linked to top-down control [11]. In tasks with humans as participants, there are also responses that can be interpreted by the occasion setter. For example, when participants need to respond correctly to an ambiguous word given the conditional cues provided by the semantic environment. Moreover, the group with high schizophrenic traits performed poorly on the biconditional discrimination task, however no poor performance was found on the simple associative task. On the first hand, the differences in performance suggest the existence of different cognitive processes in the two tasks, and people with high schizotypy traits were shown to show impairment in executive functioning[12], which is likely to be one of the reasons for their poor performance in biconditional discrimination. All of the above demonstrates that tasks involving an occasion setting require the involvement of higher cognitive processes.

In summary, it is essential to investigate the ability of patients infected with covid-19 to regulate their behaviour through occasion setter. We used the biconditional discrimination task to test participants. If people with reinfect covid-19 have reduced performance in the presence of the biconditional discrimination tasks compared to people who are not infected or infected only once, this may further affect their daily life. For comparison, we also included the simple associative task, in which individuals engage in simpler associative learning and only need to recognise the association between a stimulus and a stimulus. Additionally, we also consider the influence of some other factors

mentioned previously on the cognitive function of patients, such as age, disease severity and vaccination, and these variables are also discussed in this study.

Based on the above, the research hypothesis is that:

1) participants with reinfections are likely to make more errors in the task than the group with no covid infection and those infected only once.

2) The difference in performance on the biconditional discrimination task will be greater for participants with different numbers of infections than for the simple associative task.

3) age, number of vaccinations, and severity of infection with covid-19 are all associated with task performance.

2. STUDY

A 3x2x2x4 mixed design was used for the experiment. The number of infections was a between-subjects variable, divided into three levels, never infected, once infected, and twice infected. The experiment type was a within-subjects variable, with a biconditional discrimination task and a simple associative task. Block was a within-subjects variable with four levels and was used to examine participants' performance across different blocks .

(1) Method

Participants

Sixty-six participants completed the experiment through word-of-mouth recruitment and posting of advertisements. Excluding the 5 participants who prefer not to say their ages, the age of the remaining 61 participants ranged from 17 to 50, Mage=26.45. None of the participants had previously performed an experiment involving an occasion setting.

Experimental materials

The experiments included visual and audio stimuli, and the audio stimuli were obtained from the website. The pictures were fractals, including four colour picture files as features (orange, green, blue and red, respectively). Features were presented in visual mode with four different colour patterns, namely orange, green, blue, and red. The target was presented in auditory mode with four audio segments. In order to prevent possible confusion of participants and to balance the possible different sensitivities of the participants to colour, there are four versions of the experimental section, with the green and orange stimuli appearing in one experimental task and the blue and red stimuli appearing in another task, with the need to distinguish between the two different OS corresponding to the target in the biconditional task and not in the simple task.

Procedure

All procedures were completed online. There were two parts. Firstly, participants were asked to complete questions about their experience with covid-19. Then they were instructed to play a game about protecting spacecraft. In this game, aliens will attack the spaceship, which is equipped with two warning defence systems developed by two companies, SHIPSAFE and SECURECRAFT, to indicate specific types of attacks. The game was divided into two parts, there were two tasks to predict the attack, a biconditional discrimination task and a simple associative task as a control condition, which corresponded to each of the two defence systems described in the previous section. Two tasks design were shown in table 1.

Table 1. experiment design

Biconditional discrimination	*Simple*
AX+ BX-	CW+ DW+
AY- BY+	CZ- DZ-

A, B, C, and D represent visual stimulus(orange, green, blue, and red), and X, Y, W, Z represent auditory stimulus; "+" means combinations that result in an attack, while "-" signifies the combinations that do not predict an attack.

Biconditional discrimination task. In the biconditional discrimination task, the feature exists as an occasion setter. Participants should understand that task-setting feature A tells them to answer "Yes" (attack) when stimulus X is presented and "No" (no attack) when stimulus Y is presented. By contrast, task-setting feature B signals they should respond “No” (No attack) when present stimulus X, while they need to respond “Yes” when stimulus Y is presented. That is, the attack is only triggered when a specific FEATURE is combined with a specific TARGET (i.e. OS1: target x→attack, OS1:target y →nothing, OS2:target y→attack, OS2:target x →nothing, OS1/OS2→nothing). The occasion setter was presented 500ms before the target, and the presentation lasted 1500ms, after which the target appeared and lasted 1500ms. During the training phase, after presenting stimulus, participants were allowed to respond by pressing a key, pressing "Y" (Yes) when they predicted an incoming attack and "N" (No) when there was no incoming attack. They received feedback on whether they had judged the response correctly or not. The feedback lasted 3000ms, so they were able to gradually learn the association between the different OS and the target. There were 32 trials.

After the feedback test was completed, the participants were asked to rate the 'attack' based on different stimuli or their combination (e.g., red pictures) via the mouse. They needed to rate to what extent the presence of these stimulus would predict the onset of an attack, on a scale of 1-5, with 1 indicating no attack at all and 5 indicating an attack. The rating ranges from 1 to 5, with 1 indicating no attack at all and 5 indicating an attack. There were 8 trials.

Simple associative task. As a control group, regardless of the existence of features C or D, participants should always react "Yes" to stimulus W and "No" to stimulus Z in the simple task(feature C/D: target w→attack, feature C/D: target z→nothing). In this task, feature and target were presented simultaneously, lasting 1500ms. There were 32 trials.

After the simple associative task, participants were also asked to evaluate different stimuli or combinations of stimuli to determine how well the stimuli presented on the screen predicted the onset of an attack. The rating ranged from 1 to 5, with 1 indicating that no attack occurred at all and 5 indicating that an attack occurred. There were 8 trials.

(2) Data analysis

Participants' performance on the task was reflected by their correct judgement of the oncoming attack, with a score of 1 if they were correct and 0 if they were wrong. There were 16 postive trials (Ax+ By+) and 16 negative trials (Ay- Bx-), and the scores of each two Ax+ By+ (or Ay- Bx-) were averaged to obtain the corresponding scores in each of the four blocks. In the questionnaire, participants who selected no covid infection were marked as 0, once as 1 and twice as 2. In addition, participants who selected "maybe" were considered to be infected in this study.

(3) Results

ANOVA. A mixed ANOVA of 3(number of infection)x2(task)x2(reinforcement: positive vs negative)x4(block) was employed to assess the effects of the three variables on task performance, where number of infection was a between-subjects variable with three levels of 0, 1 and 2.

There was not a significant main effect of number of infection, F(2,63)=3.130, MSe=0.729, p=0.051, ηp2=.09. The main effect of task was significant, F(1,63)= 48.128, p<0.01, ηp2=.433. The scores for the simple associative task group [M=0.810] were overall higher than those for the biconditional discrimination task [M=0.614]. This was expected because the association learning rules for the simple associative task were simpler and easier to learn. There was a significant main effect of reinforcement, F(1,63)=20.662, p<0.01, ηp2=.247. The higher scores in the positive group than in the negative group may indicate that the participants were more likely to acquire reinforcing associations than to inhibit non-reinforcing ones.

For block variable, the main effect was significant, F(3,61)=21.756, p<0.01, ηp2=.517. Post-hoc Bonferroni tests [at p<.05] were conducted to examine the block's effect further. The results showed that participants scored significantly lower in block1 [M=0.576] than in block2 [M=0.718], block3 [M=0.768], and block4 [M=0.786], p<0.01. Additionally, participants scored significantly lower in block2 [M=0.718] than in block4 [M=0.718].

There was a significant interaction between reinforcement and block, F(3,61)=2.935, p=0.04, ηp2=.126. In block1, scores on the positive trials (M=0.633) were significantly higher than on the negative trials (M=0.519), and this difference remained in block2, i.e. the negative trials (M=0.66) performed worse than the positive trials (M=0.777). However, this difference became less pronounced in block3 (p=0.055) and block4 (p=0.149). That is the significant difference between the participants on the positive and negative diminished to insignificant as the experimental trials progressed and the participants learned the rule.

A significant interaction between task and block was found, F(3,61)=3.875, p=0.013, ηp2=.16. Focusing on the participants' performance in the first block, pair sample t-test revealed a significant difference between block1 of biconditional discrimination task(M= 0.504) and block 1 of the simple associative task(M= 0.653). At the beginning of the task, participants performed better in the simple task than in the biconditional discrimination task (p<0.01). In block4 (i.e. the last block), pair sample t-test revealed a significant difference between biconditional discrimination task(M= 0.693) and simple task(M= 0.93). In the final stage of the task, participants still performed better in the simple task than in the biconditional discrimination task(p<0.01). As the experimental trials progressed, the difference in performance between participants on the biconditional discrimination task and the simple task became larger. Unfortunately, there was not any significant interaction between the number variable and others. See Figures 1(a) and 1(b) for details.

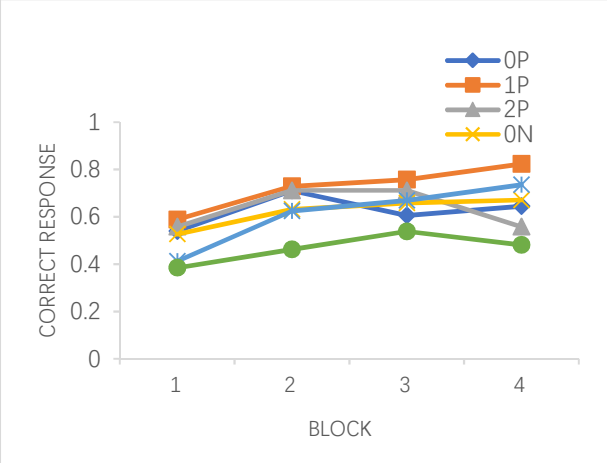

Figure 1(a). Biconditional discrimination task

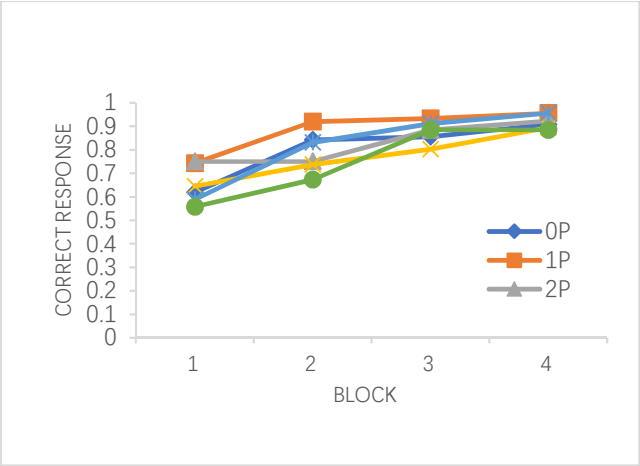

Figure 1(b). Simple associative task

0P: Performance of uninfected participants in positive trials

1P: Performance of participants who were infected once in positive trials

2P: Performance of participants who were infected twice in positive trials

0N: Performance of uninfected participants in negative trials

1N: Performance of participants who were infected once in negative trials

2N: Performance of participants who were infected twice in negative trials

Task test. 3(number of infection) x2(task test) mixed ANOVA was used to assess the effect of the two variables on the participants' scores. Results pointed to a significant main effect for the biconditional test, F (1,63) =5.039, p=0.028, ηp2=.074. The scores for the simple associative task group (M=2.023) were higher than those for the biconditional one (M=1.366). The main effect of number of infections was not significant, F (2,63) =2.459, p=0.094, ηp2=.072, which means the number of infections did not significantly affect the scores. Moreover, there was no significant interaction between the OS test and number of infections, F (2,63) =0.35, p=0.706, ηp2=.126.

Regression

Biconditional discrimination task. A hierarchical multiple linear regression was performed to predict the scores in biconditional discrimination task from number of covid-19 infections (Times), number of vaccinations (Vaccination), age and severity of infection.

Times was negatively associated with the scores of biconditional discrimination task. The participants with only once covid infection performed better and made fewer errors than those infected twice. However, the results suggested that other variables(number of vaccination, age and severity of symptoms)were not the predictor of task performance.

Simple associative task. Similarly, to the biconditional discrimination task, a hierarchical multiple linear regression was performed to predict the scores in simple task from number of covid-19 infections (Times), number of vaccinations (Vaccination), age and severity of infection.

The results showed that there was no relationship between the number of infections, number of vaccinations, age, severity of infection and performance on the simple associative task, suggesting that the relationship found in the biconditional discrimination task did not extend to the simple associative task.

3. DISCUSSION

In this study, the biconditional discrimination task was primarily used to investigate differences in the cognition of covid-19 infected. The results of the ANOVA showed that the number of infections did not significantly affect the performance of individuals on biconditional discrimination. However, the results should be treated with caution. As predicted in the hypothesis, it was evident in the regression analysis that the number of infections was associated with participants' performance on biconditional discrimination. As the number of infections increased, individuals performed more poorly on the discrimination task and made more errors. In contrast, this difference was not observed in the simple associative task. For individuals, biconditional discrimination requires a higher cognitive ability than the simple associative task, as they need to distinguish which stimuli are reinforced on each occasion setter, form specific connections, and switch between connections. The simple associative task, however, requires only a simple connection between the stimulus and the response to be learned and does not require complex processing in the brain.

Few studies of reinfection have been reported, and the complicated results of this study can be interpreted in several ways. On the one hand, because the covid-19 strain of infection may be different and may induce the same severe symptoms upon reinfection as the first infection. Participants may experience more severe cognitive impairment upon reinfection, and they may have more difficulty in performing goal-directed behaviours and learning the rules and connections in the task through situational cues. On the other hand, antibodies formed after the first infection may alleviate the symptoms during the second infection. For example, in a survey of immunocompetent reinfected Italian patients who were transferred to the ICU with their first infection, only mild symptoms developed with their second infection [13]. Therefore, it remains challenging to determine the possible impact of the number of infections on cognitive function. It is worth discussing that because impaired cognitive function due to covid-19 can be a long-term process, the possibility of reinfection also exists during the individual's recovery. Longitudinal studies could be conducted in future research investigations to compare changes in cognitive function in individuals over time and further explore the complex relationship between covid-19 and cognitive function.

No relationship was found between the three variables age, severity of infection and number of vaccinations and performance on the conditional discrimination task in this study. A possible explanation for this is that the age range of the participants in this study was only between 17 and 50 years and did not consider patients of an older age. In this age range, fewer individuals would have had the underlying disease themselves, so the difference between people might not have been significant. For the severity of people's symptoms, this study only asked participants to rate subjectively and did not assess their infection at the time by objective indicators (e.g., whether they were hospitalised). In addition, the role of the vaccine remains controversial, as the extent to which the vaccine protects against variant viral invasion of the body and how long antibodies last after vaccination need to be supported by more data in the future. In conclusion, although no relationship was found between them and performance on this task in this study, it still cannot be concluded that these three factors are not associated with covid-induced cognitive dysfunction.

In addition to the physical symptoms that occur during infection, such as fever and loss of smell and taste, the cognitive impairment caused by covid cannot be ignored. It suggested that cognitive impairment may affect up to 81% of patients after covid-19 infection[14]. In a survey of infected patients undergoing inpatient rehabilitation, a significant proportion of patients were found to have mild to severe cognitive impairment[15]. Even several months after infection, the cognitive function level remained low compared to healthy people who had not been infected. Furthermore, some studies have found that patients' attention, memory, and executive functions are impaired in terms of specific cognitive functions. For example, more than half of covid-19-infected individuals had abnormally low scores on the Frontal Assessment Battery (FAB), which used to measure executive function[16].

The causes of cognitive impairment attributed to covid-19 are multifaceted. Studies have shown that due to direct neurological damage caused by hypoxia damage or neuroinvasion, Covid-19 can also cause dysregulation of the brain's cognitive and affective functions[17]. Long-term olfactory dysfunction and cognitive decline were associated even after controlling for the effects of age, gender, and other factors[18]. Physiological events such as hypoxia may further exacerbate the neurological damage during covid infection, leading to long-term cognitive impairment[19]. In addition, cognitive symptoms may last longer and affect young people more frequently in covid-19 than in other infectious processes[20], so whether young or old, long-term cognitive impairment due to covid harms the patient's ability to return to everyday life.

In biconditional discrimination, individuals need to regulate perceived stimuli and responses to produce goal-directed behaviour. The perceptual, motor and goal representations activated during a given task interact to form a network of associations that encode the entire context overall context. The performance of conditional discrimination can also be linked to brain regions. It has been demonstrated that the correctness of conditional discrimination tasks is dependent on the prefrontal cortex[21], which is closely related to individual functions such as executive control. One study found that people after mild covid-19 responded more slowly in Stroop task[22]. According to this view, it is reasonable to assume that people infected with covid would also show impairment in biconditional discrimination, as this task requires dependence on task-set-specific cues for stimulus assessment.

There are still limitations in this study. Firstly, the sample size collected during the experiment was small, and the representation of effects may need to be expanded. Secondly, the independent variable, the number of infections sought to be explored, similar to judging severity of symptoms, was only reported in a subjective way as to whether they had been infected with covid, and how many times they had been infected. The experimenters were unaware of the results of their objective antigen test, which may have contributed to errors in the results, so this issue will need to be further controlled for in future studies. Therefore, whether reinfections have further effects on cognitive function deserves more investigation.

4. CONCLUSION

The long-term effects of covid-19 on individuals continue to be investigated. Besides the physical symptoms, the psychological and cognitive implications of covid are also essential to understand to better target patients' treatment.

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