

# Decision-making impairments in patients with Wilson's disease

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Wilson's disease (WD) causes deposition of copper, mainly in the basal ganglia. One consequence of deposition seems to be impairment of executive functions, which could cause problems in decision making. In 30 WD patients and 30 healthy controls (HCs), we examined decision making under risk in the Game of Dice Task, and we assessed working memory and executive functions. WD patients exhibited a greater preference for disadvantageous choices than did HCs. Reduced decision-making performance was closely correlated to lower executive functions. Decision-making deficits of WD might be associated with frontostriatal loops, which are involved in executive functions and feedback processing.

**Keywords:** Wilson's disease; Decision making; Game of Dice Task; Executive function; Feedback processing.

Wilson's disease (WD or hepatolenticular degeneration) is an autosomal recessive genetic disorder of abnormal copper metabolism caused by a mutation of the *ATP7B* gene, which is located on chromosome 13 (Leggio, Gasbarrini, & Addolorato, 2007). The main regions affected by copper accumulation are the liver, corneas, and brain (Leggio et al., 2007), leading to clinical manifestations, such as liver disease and neurological and psychiatric symptoms (Ferenci, 2004). After regular therapy, clinical symptoms can be gradually relieved, allowing patients to lead normal lives (Walshe, 1999). The deposition of copper may cause neuronal cell and gliocyte swelling and cystic degeneration, death, and loss, which would result in persistent neurological deficits (Ferenci, 2004).

In the brain, the majority of copper is deposited in the basal ganglia. Functional magnetic resonance imaging (fMRI) studies of WD patients have revealed abnormal signals in many brain regions, and the most common are the bilateral basal ganglia, thalamus, brain stem, and cerebellum (Alanen, Komu, Penttinen, & Leino, 1999). The dysfunction of the basal ganglia is particularly pronounced (Favrole, Chabriat, Guichard, & Woimant, 2006). The basal ganglia is usually involved in the coordination of movement and also plays a role in cognitive functions such as memory, executive functions (Monchi, Petrides, Strafella, Worsley, & Doyon, 2006), emotion recognition (Wang, Hoosain, Yang, Meng, & Wang, 2003), reward evaluation, and reversal learning (Frank, Samanta, Moustafa, &

Huijuan Ma and Xinyi Lv contributed equally to this work.

We are deeply indebted to Matthias Brand for providing the Game of Dice Task. We wish to thank the doctors and patients in the Chinese Treatment Center of Wilson's Disease for their supportive work in data collection. This work was supported by grants from the National Natural Science Foundation of China (Grants 81171273 and 31000503) and the National Basic Research Program of China (Grant 2011707805).

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Sherman, 2007). Patients with basal ganglia lesions have well-documented impairments in these cognitive functions (Frank et al., 2007; Riba, Kramer, Heldmann, Richter, & Munte, 2008).

Neuropsychological studies conducted in patients suffering from WD reported deterioration in various domains of cognition (Hegde, Sinha, Rao, Taly, & Vasudev, 2010), which could fall broadly into two main categories: frontal lobe syndromes and subcortical dementia. Frontal lobe syndromes may manifest as impulsivity, promiscuity, impaired social judgment, apathy, decreased attention, executive dysfunction, poor planning, and emotional instability. By contrast, subcortical dementia is characterized by slowness of thinking, memory loss, and executive dysfunction, without cortical signs of aphasia, apraxia, or agnosia. Certain WD patients also have a history of criminal behaviors, including arson and suicide attempts (Kaul & McMahon, 1993). Copper accumulation in specific regions of the cerebrum is believed to prevent the appropriate inhibition of such behavior. Consequently, WD patients are prone to making disadvantageous decisions. However, there are no studies that have specifically addressed decision-making performance in these patients. Our study aimed to bridge this knowledge gap because decision making is increasingly recognized as an important component of the neuropsychological characterization of WD.

Everyday life requires individuals to make many decisions. Thus, decision-making dysfunction can render much of daily life inconvenient and cause serious problems. In real life and laboratory investigations, there are two general types of decision-making situations: decisions under uncertainty and under risk. In decisions under uncertainty, no information is provided concerning the rules for gains and losses for the different options. The decider has to learn from the feedback of previous trials which alternatives are advantageous (Bechara, Damasio, Tranel, & Damasio, 2005). However, under risk situations, there is explicit information regarding the rules for gains and losses that can be ascertained from the beginning (e.g., by calculating probabilities). The decider can reason which alternatives are advantageous and which are disadvantageous in the long run without prior experience (Brand, Labudda, & Markowitsch, 2006).

Many patients with specific brain lesions and neurological diseases have been examined to understand decision making better under uncertainty and risk (Bechara, 2004; Yamano, Akamatsu, Tsuji, Kobayakawa, & Kawamura, 2011). A model of the neurocognitive mechanisms of decision making under risk was formulated by Brand et al. (Brand

et al., 2006). This model emphasized that executive functions and working memory are key functions for developing and applying advantageous strategies in risky choice situations. Furthermore, Brand posits that the processing of feedback information is also important for making good decisions.

This manuscript is focused on decision making under risk measured by the Game of Dice Task (GDT; Brand et al., 2005). The task has often been used to test the assumptions in Brand's model and for the characterization of decision-making deficits in various patient populations: Korsakoff's syndrome (Brand et al., 2005), Parkinson's disease (PD; Brand et al., 2004), Alzheimer's disease (Sinz, Zamarian, Benke, Wenning, & Delazer, 2008), temporal lobe epilepsy (Labudda et al., 2009), and restless legs syndrome (Bayard, Yu, Langenier, Carlander, & Dauvilliers, 2010). Furthermore, healthy samples were also examined (Schiebener, Zamarian, Delazer, & Brand, 2011; Starcke, Pawlikowski, Wolf, Altstotter-Gleich, & Brand, 2011). This literature provides strong evidence that GDT performance is related to executive functions, working memory, and feedback processing (Brand, Heinze, Labudda, & Markowitsch, 2008). The dorsolateral prefrontal cortex, the posterior parietal lobe, and the anterior cingulate and the right lingual gyrus have been found to be important in risky decision making (Labudda et al., 2008).

WD causes dysfunctions in brain areas that are related to the processing of emotional feedback and to executive function (Bellebaum, Koch, Schwarz, & Daum, 2008; Watson & Leverenz, 2010). The aim of the following study is to examine whether these deficits lead to impaired decision making under risk. We hypothesized that decision making under risk would be impaired in patients with WD compared with healthy control subjects. Furthermore, it is expected that the impairment will manifest as a difficulty in learning to prefer the advantageous alternatives over the task's duration (as a result of disadvantageous feedback processing) and as reduced executive abilities. We aim to enhance the neuropsychological characterization of WD and to extend the existing literature on decisions made under risk with respect to the possible roles of general executive functions and feedback processing.

## METHOD

### Subjects

Thirty patients with WD were recruited from the Anhui Neurological Institute, China. The diagnosis

of these patients was based on clinical symptoms and laboratory and imaging examination. The diagnosis criteria (Roberts & Schilsky, 2008) included (a) progressive presentation of extrapyramidal symptoms and signs in the liver; (b) corneal Kayser–Fleischer (K-F) rings observed on slit lamp examination; (c) serum ceruloplasmin  $< 20$  mg/dl or copper oxidase  $< 0.21$   $\mu$ g/dl; and (d) 24-hr urinary copper concentration  $> 100$   $\mu$ g/ml. All patients had computed tomography (CT) or MRI scans that demonstrated basal ganglia abnormality (24 of 30 had lower density on CT or lower T1 signal or high T2 signal on MRI), mild cortical or subcortical atrophy (11 of 30), and thalamus abnormality (9 of 30). All patients were receiving regular copper chelation therapy before and during the study period.

The exclusion criteria included (a) mental retardation (Wechsler Adult Intelligence Scale–Revised Chinese version IQ  $< 90$  points); (b) dysaudia and lalopathy; (c) significant liver function impairment (alanine aminotransferase  $> 100$  U or cirrhosis); (d) possible anxiety and depressive state (Hamilton Anxiety Scale, HAMA, or Hamilton Depression Scale, HAMD  $> 7$ ); and (e) treatment with L-3,4-dihydroxyphenylalanine or other drugs that affect cognition. All of the patients are evaluated using the Unified Wilson's Disease Rating Scale (UWDRS; Leinweber et al., 2008) to assess the whole clinical symptoms, including hepatic, neurological, and psychiatric clinical signs of the disease.

We also recruited 30 healthy controls (HCs) from a polytechnic school in the same region. The age, gender, and education of HCs were matched to those of the WD patients. All participants were right-handed and had normal speaking, writing, language expression, and understanding skills. Exclusion criteria of HCs were (a) Wechsler Adult Intelligence Scale–Revised Chinese version IQ  $< 90$  points; (b) a history of serious physical disorders or mental illness; (c) Hamilton Anxiety Scale (HAMA) or Hamilton Depression Scale (HAMD)  $> 7$ ; and (d) use of medicine known to influence emotion or decision making.

Before starting the task, all subjects were instructed to do their best to win as much money as possible to obtain a reward according to their final capital. Actual rewards, gifts such as a cup or a notebook, were awarded no matter how much money a subject won. The Anhui Medical University Ethics Committee approved the study protocol, and written informed consent was obtained from all participants before they entered the study.

## Background neuropsychological tasks

All participants were given a battery of neuropsychological tasks, including (a) the Mini-Mental State Examination (MMSE) to measure global cognitive functions; (b) the HAMA and HAMD to measure anxiety and depressive states; (c) the Wechsler Adult Intelligence Scale–Revised Chinese version (WAIS–RC) IQ to measure intelligence; (d) the Verbal Fluency Test (VFT; animals/water) to measure frontal functions; (e) the Digit Span test (DS; forward and backward) to estimate working memory and attention; (f) the Stroop task to measure behavior inhibition; and (g) the Wisconsin Card Sorting Test (WCST; Piper et al., 2011) to measure the general level of executive function including categorization, set-shifting, and rule recognition.

## Decision-making tasks: GDT

The GDT (Brand et al., 2005) is usually used to assess decision making under risk conditions. Participants sit in front of a computer screen watching the computer throwing dice. Before each throw, they have to guess which number will appear. They can guess a single number or a combination of two, three, or four numbers. If one of the numbers of the combination is thrown with the die, subjects will receive the associated amount of money. Conversely, the subjects will lose the same amount of money when none of the chosen numbers is thrown. As known, the winning probability of one number is  $1/6$ , and its bet is 1,000 dollars; two numbers is  $2/6$ , associated with 500 dollars; three numbers is  $3/6$ , associated with 200 dollars; and four numbers is  $4/6$  associated with 100 dollars. Each subject plays 18 trials, and the computer throws the dice in a pseudorandom manner. Subjects begin the test with a capital of 1,000 dollars. The subjects are instructed to win as much money as possible. The winning or losing of every choice will add or subtract from the starting capital and is signaled with distinct sounds and colors.

The winning probability of choosing one or two numbers is less than .5, and that of three or four numbers is .5 or higher. Therefore, we classified the first two choices as risky or disadvantageous and the last two as safe or advantageous. Choosing disadvantageous options throughout the test leads to a negative outcome; in contrast, choosing advantageous options leads to a positive outcome over the course of the test.

We calculated data as follows: (a) final capital; (b) the frequency of choosing disadvantageous and advantageous options (we also recorded the number of times that each of the four possible options was chosen); (c) utilization of negative feedback: If subjects selected a disadvantageous option (one number or the combination of two numbers) and received a loss and then chose an advantageous option immediately in the next trial, we identified the behavior as “using negative feedback.” On the contrary, if subjects chose a disadvantageous option immediately after receiving a loss for a disadvantageous option, we identified the behavior as “not using negative feedback.” The utilization of negative feedback is the frequency with which money was lost after choosing a disadvantageous option divided by the frequency of using negative feedback. Note that if subjects never chose any of the disadvantageous options or never received a loss after choosing a disadvantageous option, these data were excluded.

## RESULTS

### Results of the neuropsychological test battery

Demographic data and results from the neuropsychological test battery are shown in Table 1.

Independent *t* tests confirmed that no significant differences in age, education, MMSE, HAMA, or HAMD were observed between the WD and HC groups. A significant difference was found in the total score of the WAIS-RC IQ, but both groups had scores clearly above the cutoff. Compared to HCs, WD patients also had poorer performance on the VFT, DS (forwards and backwards), Stroop test, and WCST (as shown in Table 1).

### Decision making in the GDT

#### Final capital

Independent *t* tests were used to investigate whether the WD and HC groups differed in final capital. The final capital of the WD patients was significantly lower than that of HCs (WD:  $M = -2,093.33$ ,  $SD = 3,635.83$ ; HC:  $M = 516.67$ ,  $SD = 1,595.70$ ;  $t = -3.60$ ,  $p = .001$ ).

#### GDT choices

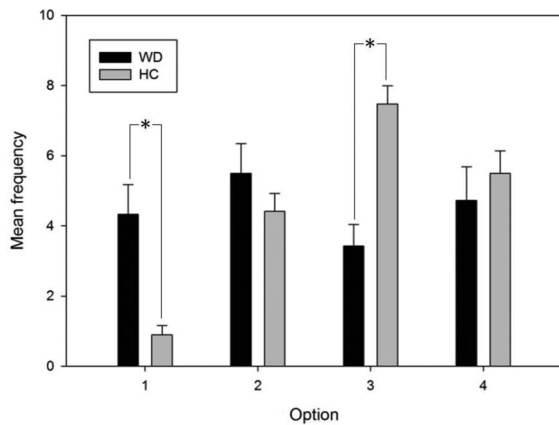
Independent *t* tests were used to investigate differences in the selection of disadvantageous options during the GDT. WD patients showed a greater preference for disadvantageous options than did the HCs (WD:  $M = 9.87$ ,  $SD = 5.95$ ; HC:  $M = 5.00$ ,  $SD = 3.35$ ;  $t = 3.91$ ,  $p < .001$ ).

**TABLE 1**  
Demographic and background data of Wilson's disease patients and healthy controls

	WD group ( $N = 30$ : 16 women/14 men)	HC group ( $N = 30$ : 16 women/14 men)	<i>p</i>
Age at investigation (years)	21.37 (3.74)	21.33 (2.52)	.214
Years of school education	10.30 (2.22)	11.10 (1.56)	.111
Duration of illness	5.40 (3.06)	—	—
UWDRS	27.45 (21.47)	—	—
MMSE	28.63 (1.30)	29.07 (0.98)	.15
VFT	12.41 (4.20)	14.59 (3.64)	.036*
DS			
Digits forwards	7.50 (0.68)	7.90 (0.31)	.005*
Digits backwards	4.07 (0.74)	5.13 (0.90)	.001*
Stroop test (s)	16.98 (13.35)	8.81 (6.17)	.049*
HAMA	2.20 (2.11)	2.50 (0.86)	.473
HAMD	2.40 (2.40)	2.60 (0.67)	.662
WCST			
Categories completed	6.77 (1.88)	8.0 (1.03)	.033*
Perseverative errors (per)	34.69 (3.59)	11.80 (2.81)	.001*
Nonperseverative errors (per)	14.78 (5.03)	8.05 (4.20)	.001*
WAIS-RC	97.82 (6.79)	111.7 (5.64)	.001*

*Notes.* Means; standard deviations in parentheses. max = maximum; per = percentiles; s = seconds. WD = Wilson's disease; HC = healthy control; DS = Digit Span test; HAMA = Hamilton Anxiety Scale; HAMD = Hamilton Depression Scale; MMSE = Mini-Mental State Examination; UWDRS = Unified Wilson's Disease Rating Scale; VFT = Verbal Fluency Test; WAIS-RC = Wechsler Adult Intelligence Scale-Revised Chinese version; WCST = Wisconsin Card Sorting Test. Significant differences between the WD group and HC group are indicated with an asterisk.





**Figure 1.** WD patients selected two-number combinations most frequently, and HCs were more likely to select three-number combinations. Single comparisons between the groups revealed significant differences in the frequency for choosing one single number and three numbers but not in two numbers and four numbers.

Additionally, we compared how often each of the four options was chosen by the WD patients and the HCs. We conducted an analysis of variance with repeated measurements with “choice” as the within-subject factor and “group” as the between-subject factor. There was a significant main effect for choice,  $F(3, 174) = 6.59$ ,  $MSE = 98.39$ ,  $p = .002$ , and a significant interaction of Choice  $\times$  Group,  $F(3, 174) = 7.94$ ,  $MSE = 153.02$ ,  $p = .001$ . WD patients selected two-number combinations most frequently, and HCs were more likely to select three-number combinations. Single comparisons between the groups revealed significant differences in the frequency for choosing one single number (WD:  $M = 4.33$ ,  $SD = 4.64$ ; HC:  $M = 0.90$ ,  $SD = 1.40$ ;  $t = 3.88$ ,  $p < .001$ ) and three numbers (WD:  $M = 3.43$ ,  $SD = 3.34$ ; HC:  $M = 7.47$ ,  $SD = 2.85$ ;  $t = -5.03$ ,  $p < .001$ ), but mean frequency of two numbers (WD:  $M = 5.50$ ,  $SD = 4.58$ ; HC:  $M = 4.10$ ,  $SD = 2.78$ ;  $t = 1.41$ ,  $p = .16$ ) and four numbers (WD:  $M = 4.73$ ,  $SD = 5.24$ ; HC:  $M = 5.50$ ,  $SD = 3.52$ ;  $t = -0.67$ ,  $p = .51$ ) did not reach statistical significance (as shown in Figure 1).

### Utilization of negative feedback

Compared with the HC group, the WD group made less use of negative feedback (WD:  $M = 0.34$ ,  $SD = 0.31$ ; HC:  $M = 0.78$ ,  $SD = 0.23$ ;  $t = -0.97$ ,  $p < .001$ ), meaning that even after losing 500 or 1,000 dollars, WD patients continued to make disadvantageous choices. Conversely, when HCs received persistent negative feedback in a trial, they more often changed their behavior to select an advantageous option for their next choice. This

behavior may have led to their improvement over the duration of the entire task.

### Correlation analysis

Additionally, in the WD group, the frequency of disadvantageous choices was highly correlated with the WCST (categories completed:  $r = -.784$ ,  $p = .002$ ; perseverative errors:  $r = .718$ ,  $p = .006$ ). All other correlations with background neuropsychological tasks failed to reach significance. Furthermore, the GDT performance of WD patients was not correlated with years of school education ( $r = -.099$ ,  $p = .603$ ), duration of illness ( $r = -.092$ ,  $p = .623$ ), total UWDRS score ( $r = .17$ ,  $p = .63$ ), or IQ ( $r = -.093$ ,  $p = .732$ ).

### IQ inference

IQ matching is notably important in studies on cognitive function in patients with brain damage. To analyze the effect of IQ on GDT performance, we added it as a covariate in the repeated measures analysis of variance (ANOVA) of “Choice  $\times$  Group.” The interaction between group and choice was still significant ( $F = 3.34$ ,  $p = .05$ ) after including the IQ covariate. Moreover, IQ did not have a significant effect on the disadvantageous choices in the GDT ( $F = 0.65$ ,  $p = .6$ ), group ( $F = 0.07$ ,  $p = .79$ ), and Choice  $\times$  Group ( $F = 2.80$ ,  $p = .09$ ) either.

## DISCUSSION

Our study used the GDT with WD patients as well as healthy controls to examine decision making with explicit and stable rules for gains and losses.

The main finding of our study is that WD patients have impairments in decision making under risky conditions. Compared with HCs, WD patients not only make more disadvantageous choices, but also use less negative feedback. Therefore, our results support the notion that executive functions and feedback processing play a key role in decision making under risky conditions (Brand et al., 2009; Schiebener et al., 2011). Suitably, in a neuropsychological test battery, we also found that WD patients exhibited poorer performance in frontal functions, such as attention, working memory, behavior inhibition, and the general level of executive functions.

Based on correlations discovered in neuropsychological research using the GDT, Brand formulated a model of the potential relationship between feedback processing, executive function,

and decision making under risky conditions (Brand et al., 2006). The model describes two parallel but correlative dependencies involved in making decisions under these conditions: cognitive and emotional. A large number of studies have examined the cognitive and emotional processes involved in decision making.

Executive functions related to GDT performance include set shifting, concept formation, and interference susceptibility (Brand, Roth-Bauer, Driessen, & Markowitsch, 2008; Starcke et al., 2011). Emotional feedback processing is correlated with GDT performance and plays a key role in decision-making performance (Brand, 2008; Brand et al., 2009). In our experiment, WD patients also experienced difficulty in WCST and in using negative feedback. Consequently, we speculate that decision-making deficits may be a result of disadvantageous feedback processing and reduced executive abilities.

The precise contributions of specific brain areas to the decision-making abnormalities in WD remain a matter of debate. However, it is likely that areas related to executive function and emotional processing are especially relevant. In the brain of WD patients, excessive copper accumulates primarily in the basal ganglia. These changes affect the function of the frontostriatal networks, which are involved in motor, cognitive, emotional, and motivated behavior (Swainson et al., 2000). The dorsal component of the prefrontal lobe (PFC) is connected with the dorsal striatum, which is a key structure that contributes to executive function. Therefore, patients with basal ganglia impairment tend to exhibit executive dysfunction. Patients with PD and Huntington's disease have shown impairment of executive function associated with striatum atrophy (Dirnberger, Frith, & Jahanshahi, 2005; Peinemann et al., 2005). In our experiment, WD patients demonstrated poor performance in the WCST and Stroop test, which are classic tasks for investigating general executive function. These results are consistent with the results of previous studies of basal ganglia dysfunction. The ventral portion of the PFC is also connected with the ventral striatum, which is involved in emotion and reward processing (Jahanshahi et al., 2010). Previous studies of patients with PD and Huntington's disease have documented impairment in emotion recognition, feedback, and reward processing (Frank et al., 2007; Wang et al., 2003). In the present study, we also find that compared with HCs, WD patients use less negative feedback to improve their behavior.

In reality, the neural injuries in WD patients are not restricted to the basal ganglia (24 of 30 had

lower density on CT or lower T1 signal or high T2 signal on MRI in our study), but are also present in the thalamus, brain stem, and cerebellum. The thalamus, along with the basal ganglia, is part of the cortical–basal ganglia–thalamic circuits, which affect motivation, emotion processing, planning, and memory (Cheng, Tian, Hu, Wang, & Wang, 2010; Haber & Calzavara, 2009). The notion that the cerebellum is involved in multiple domains of cognitive function has become widespread in recent decades. Patients with cerebellar injuries often exhibited deficits of language, executive function, and time perception (Fierro et al., 2007; Stoodley & Stein, 2011). Brain stem is thought to be involved with alertness, awareness, and consciousness. Therefore, we could not conclude from our study that WD patients have difficulty in decision making under risky conditions exclusively because of their basal ganglia lesions. However, we assume that WD patients with basal ganglia lesions have most likely impaired executive functions and feedback processing, which could lead to problems with decision making.

Intelligence seems to be important to decision making, especially in the Iowa Gambling Task (IGT; Labudda et al., 2009; Levine et al., 2005). The effect of intelligence on GDT has not previously been demonstrated. In our study, HCs obtained much higher scores than WD patients, but we did not discover any correlation between GDT performance and IQ. And IQ has no significant effect as covariate either. Therefore, impairment of decision making under risk in the WD patients is not due to reduced IQ.

## CONCLUSION

To the best of our knowledge, this study is the first to investigate the decision-making abilities of WD patients under risky conditions. Our results will enhance the neuropsychological characterization of WD and extend the literature detailing decisions made under risk conditions with respect to the possible roles of general executive functions and feedback processing. These results also provide evidence for the relevance of the basal ganglia for making decisions. Particularly, basal ganglia dysfunctions impair executive function and feedback processing, which could lead to problems with decision making.

## LIMITATION

The interpretation of our results is somewhat limited by the fact that the injuries in WD patients

were not limited to the basal ganglia. Therefore, we cannot totally exclude the possible influence of other damaged regions in altering decision-making behavior. In the future, we will attempt to select patients with localized basal ganglia lesions to minimize the influence of any other regions in our results.

Original manuscript received 4 April 2012  
Revised manuscript accepted 21 March 2013  
First published online 24 April 2013

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