Original Paper

Modafinil alters decision making based on feedback history – a randomized placebo-controlled double blind study in humans

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Abstract

Modafinil is becoming increasingly popular as a cognitive enhancer. Research on the effects of modafinil on cognitive function have yielded mixed results, with negative findings for simple memory and attention tasks and enhancing effects for more complex tasks. In the present study we examined whether modafinil, due to its known effect on the dopamine level in the striatum, alters feedback-related choice behaviour. We applied a task that separately tests the choice of previously rewarded behaviours (approach) and avoidance of previously punished behaviours. 18 participants received a single dose of 200 mg modafinil. Their performance was compared to a group of 22 participants who received placebo in a double-blind design. Modafinil but not placebo induced a significant bias towards approach behaviour as compared to the frequency of avoidance behaviour. General attention, overall feedback-based acquisition of choice behaviour and reaction times in high vs low conflict choices were not significantly affected by modafinil. This finding suggests that modafinil has a specific effect on dopamine-mediated choice behaviour based on the history of feedback, while a contribution of noradrenaline is also conceivable. The described change in decision making cannot be considered as cognitive enhancement, but might rather have detrimental effects on decisions in everyday life.

Keywords

Modafinil, reward, punishment, learning

Introduction

The term neuroenhancement refers to healthy people's attempts to improve cognitive functions by means of psychoactive drugs. According to recent investigations, a considerable number of people use a prescription or illicit drug as a cognitive enhancer (CE; Franke et al., 2014). Prevalence rates vary, however, between 1% and 20% depending on the country, the study population and the type of questionnaire used (Dietz et al. 2013; Franke et al. 2011; Teter et al. 2006).

Among the most popular CE substances is modafinil, which has been developed for promoting wakefulness in the sleep disorder narcolepsy. Findings on the efficacy of a single dose of modafinil on cognitive function in healthy participants are mixed. Based on a meta-analysis, Repantis and colleagues (2010) reported that in rested individuals only effects on attention were significant. Battleday et al. (2015) distinguished between simple and complex tasks, with simple tasks testing one or two particular cognitive functions, mostly (but not always) by means of standardized neuropsychological tests. For both attention and memory tasks no clear pattern of improvement after modafinil intake emerged (Marchant et al., 2009; Muller et al., 2004, 2013; Randall et al., 2003, 2004, 2005a,b; Turner et al., 2003; Winder-Rhodes et al., 2010). The findings concerning inhibitory control and working memory were also inconsistent (Franke et al., 2014; Muller et al., 2004, 2013; Turner et al., 2003), but for higher functions, such as planning processes, improvements by modafinil were reported (Muller et al., 2004, 2013). Similarly, modafinil elevated performance in complex laboratory tasks (Finke et al., 2010; Geng et al., 2013; Marchant et al., 2009; Pringle et al., 2013) involving higher attentional or executive functions, probably mediated by top-down mechanisms related to prefrontal processing (Battleday and Brem, 2015; Esposito et al., 2013; Minzenberg et al., 2008).

Investigations on its pharmacological effects have shown that modafinil affects several neurotransmitter systems. By inhibiting catecholamine transporters, it particularly increases the extracellular levels of dopamine (DA) and noradrenaline (NA; Kim et al., 2014; Madras et al., 2006; Volkow et al., 2009;), which have both been linked to reward processing and decision making. While for NA and the NA-producing locus coeruleus (LC) functions such

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as shifting between exploration and exploitation (Aston-Jones and Cohen, 2005) and energization of behaviour (Varazzani et al. 2015) are discussed, striatal DA is known to play a key role in reward processing and feedback-based behavioural adaptation (Bodi et al., 2009; Cools et al., 2006; Frank et al., 2004; Schultz et al., 1997; van der Schaaf et al., 2014; Zaghloul et al., 2009). Thus, it is conceivable that modafinil interferes with these processes in healthy human participants. Indeed, Funayama et al. (2014) recently observed higher nucleus accumbens activity during reward anticipation under modafinil than under placebo, suggesting that modafinil affects processing in DA pathways. Behavioural effects of modafinil on specific DA-mediated decision processes have, however, not been systematically investigated to date.

In Parkinson's disease (PD), medication elevating the DA level has repeatedly been shown to induce a bias towards choosing previously rewarded stimuli (approach behaviour) compared to avoiding previously punished stimuli (avoidance behaviour), which has been related to a bias in reward vs punishment processing and learning (Bodi et al., 2009; Cools et al., 2006, 2009; Frank et al., 2004; Pessiglione et al., 2006; van der Schaaf et al., 2014; Voon et al., 2010,) or a bias in response selection (Shiner et al., 2012; Smittenaar et al., 2012). In everyday life, however, increased reward seeking behaviour might have adverse consequences. For example, pathological gambling and other impulse control disorders are frequently seen as a consequence of medication in PD (Moore et al., 2014; Pirritano et al., 2014; Weintraub et al., 2015). Although, as mentioned, effects on other neurotransmitter systems cannot be excluded, the present study aimed to specifically test the consequences of modafinil intake on behaviour related to the DA system by using a specific feedback learning task applied in PD patients and other populations previously (Chase et al., 2010; Frank et al., 2004; 2007; Kobza et al., 2012; Solomon et al., 2015; Whitmer et al., 2012). We hypothesized that a single dose of modafinil induces a bias towards previously rewarded choices relative to the avoidance of previously punished choices in healthy participants, which would have important implications for the debate on potential neuroenhancing effects of this substance. To this end, we examined choice behaviour based on the history of the associated feedback under modafinil and placebo in a double-blind between-subjects design.

Methods

Participants

In total, 40 healthy, non-sleep-deprived young men between 18 and 40 years of age volunteered to participate in this study on feedback learning. Exclusion criteria were history of neurological or psychiatric disorder or substance abuse, any medication within the last four weeks (all assessed by means of a structured interview), regular nicotine consumption and an IQ below 85 (assessed by means of a German version of the vocabulary test; Lehrl et al., 1995). Furthermore, participants were asked to refrain from alcohol in the last 24 h before testing. Immediately before testing, participants were screened for current drug consumption by means of a urine test covering cannabinoids, benzodiazepines, opiates, cocaine and amphetamines. Finally, the Beck Depression Inventory (BDI, Hautzinger et al., 2009) was used as a measure for current depressive symptoms.

Each participant was randomly assigned to one of two treatment groups, one receiving a single dose of 200 mg modafinil, the other receiving placebo. Neither the participant, nor the experimenter was informed about treatment group assignment. Of the 40 participants, 22 received placebo and 18 modafinil. Three of the 40 participants (two treated with modafinil and one with placebo) had to be excluded from data analysis: one had an elevated BDI total score indicating depressive symptoms, one had a positive drug screening and one revealed that he knew the meaning of some of the Asian stimuli used in the experiment (see below). The remaining 21 participants of the placebo group were on average 24.7 years old (SD=3.3), whereas the remaining 16 participants treated with modafinil were on average 25.0 years old (SD=4.8). Mean scores for verbal IQ amounted to 113 for both groups (SD=10 for participants under placebo and SD=12 for participants under modafinil).

Alertness task

To assess basic attentional functions, the test 'alertness' was administered (Zimmermann and Fimm, 2007). In this test, participants have to respond as fast as possible to a visual target stimulus ('tonic alertness'). On half of the trials, presented in separate blocks, the target stimulus is preceded by a warning tone, typically resulting in faster reaction times ('phasic alertness').

Feedback learning task

A variant of the probabilistic selection task described by Frank et al. (2004) was used as the feedback learning task, programmed in presentation software (Neurobehavioral Systems, Inc.). On each trial in the learning phase, participants were asked to choose between two non-verbalizable Asian stimuli presented on the left and right side of a computer screen, respectively. After their choice, participants were given positive or negative feedback concerning choice accuracy ('correct' or 'wrong'), which will be referred to as reward and punishment in the following. Six different stimuli could appear in the task, referred to as A–F. The stimuli appeared in fixed pairs – A and B, C and D, E and F – which differed with respect to feedback probabilities. For the AB pair, choosing A or B led to reward in 80% or 20% of the trials and to punishment in the remaining trials. For CD and EF the probabilities were 70% vs 30% and 60% vs 40%.

The task consisted of four learning sessions with 60 trials each, 20 per stimulus pair. Each learning phase was followed by a test phase. The trials of the test phase presented the same stimulus pairs, but without participants receiving feedback for their choices (see Kobza et al., 2012). The test phases thus aimed to assess whether participants kept responding according to the learned stimulus-associated feedback probabilities even in the absence of trial-by-trial feedback. The test phases entailed 30 trials, 10 per stimulus pair. For both the learning and test phases responses were considered correct if participants chose the stimulus with the higher reward probability (irrespective of the feedback in the particular trial in the learning phase).

Following the fourth test phase, all participants entered a transfer phase of 40 trials, in which new stimulus combinations were presented, pairing the 'best' stimulus A or the 'worst' stimulus B with one of the other stimuli (combinations AC, AD, AE,

AF, BC, BD, BE, BF). The participants were again asked to choose the 'correct' stimulus in each pair, without receiving feedback for their choices. The sums of A choices and non-B choices in the transfer phase were the dependent variables. As in numerous other studies applying variations of this paradigm (e.g. Chase et al., 2010; Frank et al., 2004; 2007; Kobza et al., 2012; Solomon et al., 2015; Whitmer et al., 2012), the interpretation in terms of approach or avoidance behaviour was based on the comparison of these two variables. More frequent choices of stimulus A than avoidances of stimulus B in the respective trials were considered to reflect a preference for previously rewarded choices, whereas the opposite pattern was considered as an indicator for a preference against previously punished choices, with the former reflecting a specific type of impulsivity.

In order to examine if decision making was generally altered under modafinil, a second measure was derived from the transfer phase, targeting a different type of impulsive responding. More specifically, reaction times (RTs) were derived separately from high and low conflict trials, that is, trials involving stimuli with comparable (AC, AE, BD and BF) or quite different (AD, AF, BC, BE) probabilities of positive (and thus also negative) feedback. Typically, RTs are enhanced for high compared to low conflict trials. Impulsivity in terms of speeded responses for high conflict trials has been reported in Parkinson's patients undergoing deep brain stimulation of the subthalamic nucleus (Frank et al., 2007).

Finally, the general ability to learn stimulus–outcome associations was examined by analysing choice accuracy across blocks during the learning phases. Importantly, transfer phase performance could only be interpreted if participants learned to choose stimulus A over stimulus B in the learning phase. Therefore, participants had to reach a learning criterion to enter analysis of the transfer phase (see Results section).

Procedure

Testing was conducted in the LWL University Hospital of the Ruhr University Bochum, Germany. When participants came into the laboratory, they were given detailed information about the study and about behavioural testing. After they had signed an informed consent form, a urine sample was collected from the participants and the drug screening was conducted. Then, oral study medication was given, together with a glass of water. Each subject was administered with either modafinil (200 mg) or placebo in the form of identical-looking white tablets. The tablets were given to the participants by the study physician (PR) according to a previously created randomization list. The experimenter was neither informed about the type of medication given to the participant, nor had she access to the randomization list. Also, the participants were not told what type of medication they received. Considering the pharmacokinetic profile of modafinil, behavioural testing started after two hours from medication intake for all participants. At the beginning of the waiting time participants filled in the BDI questionnaire and completed the IQ test. In the remaining time they were allowed to read or study, while blood pressure was monitored regularly. Behavioural testing started with the alertness task, then the feedback learning task was conducted. The study was approved by the Ethics Committee of the Medical Faculty at Ruhr University Bochum and was conducted in accordance with the ethical standards laid down in the Declaration of Helsinki.

Statistical analysis

Reaction time data from the alertness test entered a repeated measures analysis of variance (ANOVA) with the factor Warning Tone (yes, no) and the between-subjects factor Treatment Group (modafinil, placebo). Accuracy across blocks during the learning phases of the feedback learning task was analysed by an ANOVA with the between-subjects factor Treatment Group and the within subjects factors Stimulus Pair (AB, CD, EF) and Block (1–4). For performance accuracy in the transfer phase a repeated-measures ANOVA with the factors Treatment Group and Choice Type (approach, avoid) was conducted. Finally, the factors Treatment Group and Conflict (high, low) entered an ANOVA for RTs in the transfer phase. For all analyses, the p-value for statistical significance was set to $p<0.05$. Greenhouse–Geisser corrections were conducted where appropriate. Significant interactions were further analysed with post-hoc t-tests, for which the significance level was adjusted for multiple testing.

Results

Tonic and phasic alertness

The analysis of tonic and phasic alertness revealed mean reaction times of 290 ms (SD=28 ms) and 300 ms (SD=42) for participants under placebo and modafinil, respectively, in the condition without warning tone. When visual stimuli were preceded by a warning tone, reaction times slightly decreased (mean of 283 ms, SD=26 ms for placebo; mean of 289, SD=38 for modafinil), which was reflected in a near significant effect of Warning Tone ($F(1,38)=3.583$; $p=0.066$). Neither the main effect of Treatment Group, nor the Treatment Group by Warning Tone interaction approached significance (both $p>0.40$).

Learning phase of the feedback learning task

Figure 1 shows the learning curves for the different stimulus pairs in both treatment groups. Although participants under modafinil generally scored higher on performance accuracy compared to placebo, the effect was not significant ($p=0.124$ for the main effect of Treatment Group). Across Treatment Groups a significant increase in performance accuracy from block 1 to 4 was seen (linear trend: $F(1,35)=27.652$; $p<0.001$) as well as a main effect of Stimulus Pair ($F(2,70)=4.177$; $p=0.019$), indicating that performance accuracy reflected the different degrees of difficulty for each stimulus pair resulting from the different reward probabilities. None of the two- or three-way interactions reached significance (all $p>0.400$).

Transfer phase of the feedback learning task

As outlined above, transfer phase performance can only be interpreted for participants who reached a certain performance level at the end of the learning phase, which was set to 14 out of 20 possible correct responses in the last learning phase, equalling an accuracy level of 70%. At the same time, the transfer phase required that participants keep responding according to the learned reward probabilities, also in the absence of trial-by-trial feedback. We therefore included only those participants, who also reached 70% correct responses for the AB pair in the last test

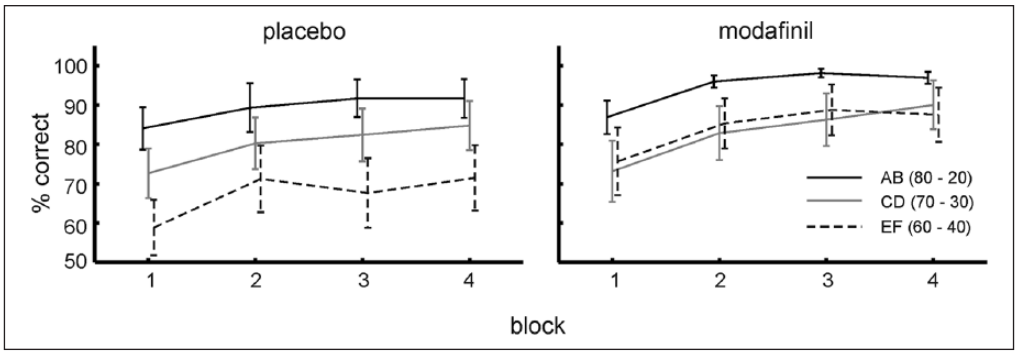

Figure 1. Learning curves for participants under modafinil and placebo for all three stimulus pairs.

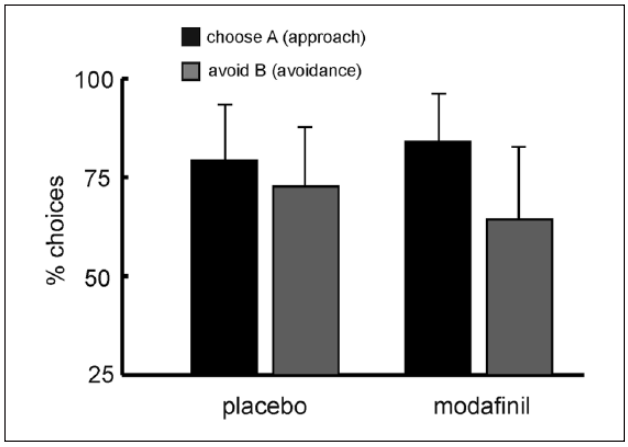

Figure 2. frequency of choices indicating approach (choose A) or avoidance behavior (avoid B) in the modafinil and placebo treatment groups.

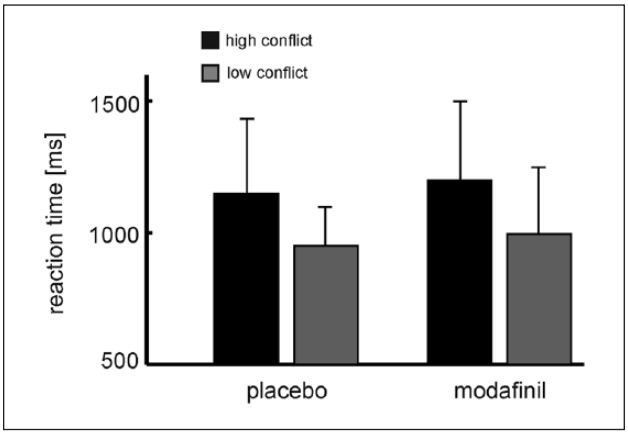

Figure 3. Reaction times for high and low conflict trials in the transfer phase in participants under modafinil and placebo.

phase, which, like the transfer phase, did not entail feedback. All but one participant under placebo reached these criteria, so that the analysis of transfer phase performance was based on 20 participants in the placebo group and 16 in the modafinil group.

Figure 2 shows performance accuracy in the transfer phase, separately for trials requiring the choice of previously rewarded stimuli or the avoidance of previously punished stimuli and for the two Treatment Groups. While the two groups did not generally differ in performance (p=0.654), the scores for choosing rewarded stimuli (approach) were higher than those for avoiding punished stimuli (main effect Choice Type: F(1,34)=17.303; p<0.001). Finally, the interaction between both factors also reached significance (F(1,34)=4.388; p=0.044). Descriptively, approach behaviour was increased and avoidance behaviour decreased under modafinil compared to placebo. Direct comparisons between the treatment groups did not reach significance (both p>0.140). Separate analyses in the two groups revealed, however, that participants under modafinil showed a highly significant bias for more approach than avoidance behaviour (t(15)=4.085; p=0.001), while no significant bias was seen for participants under placebo (p=0.130).

The analysis of transfer phase RTs revealed a significant conflict effect F(1,34)=23.196; p<0.001). RTs were generally longer for high than low conflict trials (see Figure 3). The main effect of Treatment Group and the interaction of both factors did not reach significance (both p>0.525).

Discussion

The use of illicit or prescription drugs has become increasingly popular among healthy people for the purpose of cognitive enhancement (Franke et al., 2014). Empirical evidence for cognitive enhancing effects of one of the most frequently used substances, modafinil, is sparse (Battleday and Brem, 2015; Marchant et al., 2009; Muller et al., 2004, 2013; Randall et al., 2003, 2004, 2005a,b; Turner et al., 2003; Winder-Rhodes et al., 2010). Modafinil has been shown to increase extracellular levels of DA and NA by blocking dopamine and noradrenaline transporter activity (Kim et al., 2014; Madras et al., 2006; Volkow et al., 2009). While both neurotransmitters appear to be involved in decision making (Aston-Jones und Cohen, 2005; Frank et al., 2004; Varazzani et al., 2015), the role of DA has been well described in numerous studies with different species and methods. For example, single DA neurons code a reward prediction error in both monkeys and humans, (Schultz et al., 1997; Zaghloul et al., 2009). Medication targeting the DA level has been shown to induce a bias towards previously rewarded choices compared to the avoidance of previously punished choices in PD (Frank et al., 2004; Shiner et al., 2012; Smittenaar et al., 2012), which has been linked to a

'DA overdose' in parts of the striatum (Kish et al., 1988). Also, in healthy humans, striatal DA has differential effects on learning from rewards and punishments (Cools et al., 2009; Jocham et al., 2011; Pessiglione et al., 2006; van der Schaaf et al., 2014). We therefore hypothesized that modafinil, due to its effect on the DA system, would lead to an imbalance between approach and avoidance behaviour. In accordance with this assumption, we observed a choice bias in favour of previously rewarded choices in healthy young men after they had taken a single dose of 200 mg modafinil. No such bias was seen in a placebo control group. Remarkably, modafinil affected neither feedback learning in general, nor RTs in high or low conflict choices or in a simple reaction time task assessing tonic and phasic alertness, suggesting that modafinil specifically alters certain aspects of (choice) behaviour.

The mechanisms leading to such a behavioural bias are the matter of an ongoing debate. First described by Frank et al. (2004) in PD, the bias was interpreted in terms of better learning from positive than negative feedback. With elevated DA levels, the DA dips typically seen after negative feedback or punishment (Schultz et al., 1997) were considered not strong enough to establish links between stimuli or actions on the one hand and negative consequences on the other. More recent studies have suggested that the bias in choice behaviour reflects changes in action selection rather than learning (Shiner et al., 2012; Smittenaar et al., 2012) given the prominent role of the striatum in response criterion setting (Forstmann et al., 2008; Kuchinke et al., 2011). On the other hand, drugs affecting DA transmission in healthy humans have been shown to alter striatal responses also during learning (Jocham et al., 2011; van der Schaaf et al., 2014). Modafinil effects on reward-related processes in healthy participants are just beginning to be explored. The recently reported enhanced nucleus accumbens activity for reward anticipation under modafinil might at least suggest that altered learning processes have contributed to the present findings (Funayama et al., 2014). The biases in choice behaviour seen under modafinil in the present study might thus result from effects on learning or response selection, or a combination of both.

At the same time, modafinil not only elevates the DA level, but also affects NA and other neurotransmitter systems (Madras et al., 2006; Volkow et al., 2009). While NA has traditionally been associated with arousal (Berridge and Waterhouse, 2003), more recently an involvement in different processes relevant for decision making has been proposed. In the adaptive gain theory, tonic vs phasic modes of LC firing have been hypothesized to underlie different behavioural states. The phasic mode is characterized by enhanced responses to relevant stimuli aiming at the optimization of performance in the task at hand in terms of reward maximization. The tonic mode facilitates processing of both task-relevant and task-irrelevant stimuli, thereby promoting task disengagement and exploration (Aston-Jones and Cohen, 2005). In another account based on single cell recordings in behaving monkeys, Varazzani et al. (2015) suggested complementary roles of DA and NA in decision making, with NA coding the difficulty of the upcoming task in order to provide the necessary resources for meeting the challenge. Although the task used in the present study was designed to assess effects of altered DA levels, it is conceivable that modafinil effects on the NA system contributed to the pattern of findings. Minzenberg et al. (2008) have demonstrated that modafinil shifts LC firing towards the phasic response state, which should, according to the adaptive gain theory, facilitate the processing of task relevant stimuli and exploitation. This might have facilitated the preferred processing of positive vs negative outcomes induced by elevated DA levels.

It is important to note that the pattern of altered choice behaviour found under modafinil in the present study cannot be considered as cognitive enhancement. Instead, there is reason to believe that a balanced ratio of choices that are likely to yield reward and avoiding choices that will likely result in punishment is the best strategy for behavioural adaptation. For example, a strong bias for choosing previously rewarded behaviour, while at the same time neglecting potential negative consequences, might lead to risk proneness, as can be seen in the frequent occurrence of gambling disorder in medicated PD patients, especially after treatment with DA agonists targeting D3 receptors (Pirritano et al. 2014; Weintraub et al. 2010).

As a limitation of the study one might mention that although the significant bias for approach behaviour appeared only with modafinil and not with placebo, the between-group comparisons for approach or avoidance behaviour were both not significant. Descriptively, modafinil enhanced approach and reduced avoidance learning, which gave rise to the overall bias in the pattern of choices. With a larger sample it might have been possible to elucidate if approach or avoidance is particularly altered by modafinil. Finally, DA-mediated effects of modafinil on learning for individual subjects are likely to depend on DA baseline levels in the striatum, as has been shown for dopaminergic drug effects (Cools et al., 2009).

In conclusion, the present study is the first to show alterations of reward-related behaviour induced by a single dose of 200 mg modafinil. Compared to placebo, modafinil leads to an enhanced tendency to make previously rewarded choices compared to the avoidance of previously punished choices. This pattern of altered choice behaviour, which may have detrimental effects on everyday decisions, is probably linked to altered feedback learning or response selection, or both, induced by an increase in the DA level and a potential contribution of elevated NA. Future studies will have to investigate the neural mechanisms of altered choice behaviour under modafinil with a special focus on the relative contributions of the DA and NA systems.

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