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Repetitive transcranial magnetic stimulation over dorsolateral prefrontal cortex modulates value-based learning during sequential decision-making

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A B S T R A C T

Adaptive behavior in daily life often requires the ability to acquire and represent sequential contingencies between actions and the associated outcomes. Although accumulating evidence implicates the role of dorsolateral prefrontal cortex (dlPFC) in complex value-based learning and decision-making, direct evidence for involvements of this region in integrating information across sequential decision states is still scarce. Using a 3-stage deterministic Markov decision task, here we applied offline, inhibitory low-frequency 1-Hz repetitive transcranial magnetic stimulation (rTMS) over the left dlPFC in young male adults (n = 31, mean age = 23.8 years, SD = 2.5 years) in a within-subject cross-over design to study the roles of this region in influencing value-based sequential decision-making. In two separate sessions, each participant received 1-Hz rTMS stimulation either over the left dlPFC or over the vertex. The results showed that transiently inhibiting the left dlPFC impaired choice accuracy, particularly in situations in which the acquisition of sequential transitions between decision states and temporally lagged action-outcome contingencies played a greater role. Estimating parameters of a diffusion model from behavioral choices, we found that the diffusion drift rate, which reflects the efficiency of information integration, was attenuated by the stimulation. Moreover, the effects of rTMS interacted with session: individuals who could not efficiently integrate information across sequential states in the first session due to disrupted dlPFC function also could not catch up in performance during the second session with those individuals who could learn sequential transitions with intact dlPFC function in the first session. Taken together, our findings suggest that the left dlPFC is crucially involved in the acquisition of complex sequential relations and in the potential of such learning.

Introduction

Beyond its roles in working memory and cognitive control, many studies have begun to investigate the impacts of the lateral prefrontal cortex (PFC) in more complex aspects of value-based learning and decision-making. For instance, in situations where complex task rules need to be learned or in cases when multiple facets of a decision need to be jointly considered (see Dixon and Christoff, 2014, for review). Accumulated findings from lesion (Badre et al., 2009) and functional magnetic resonance imaging (fMRI) studies (Braver and Bongiolatti, 2002; Bunge et al., 2009; Christoff et al., 2001; Koechlin et al., 2003; Smith et al., 2007) implicate regions such as the anterior and mid-dorsolateral PFC (Brodmann's areas 10, 9/46) in learning abstract task rules and mental processing of relational information. Furthermore, converging evidence from a range of electrophysiological (e.g., Shima et al., 2007) and imaging (e.g., Koechlin and Jubault, 2006) studies reveals a rostro-caudal axis of functional divisions in the frontal lobes, with the lateral PFC (particularly the mid-dorsolateral regions) being involved in various aspects of abstract rule learning, including the acquisition of sequential relations or cross-temporal contingencies for action planning (see Badre & D'Esposito, 2009, for review). Of note, other than correlational evidence from brain imaging studies, results of studies applying non-invasive brain stimulation methods lend further support for lateral PFC's roles in some of these functions.

Of particular relevance, there are findings from studies applying transcranial magnetic stimulation (TMS) to transiently disrupt or excite local neural processing. Specifically, a common approach to study TMS effects on cognitive processes is to apply a train (series) of multiple TMS pulses over several minutes, called repetitive TMS (rTMS). Depending on the frequency, intensity and type of stimulations, rTMS could transiently excite or inhibit neuronal postsynaptic potentials (Pascual-Leone et al., 2000; Schlaak et al., 2007; Ziemann and Hallett, 2007). For instance, low-frequency (1-Hz) inhibitory rTMS applied over the right inferior frontal junction (Zanto et al., 2011) or the superior frontal sulcus in the

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posterior left dorsolateral PFC (Philiastides et al., 2011) have, respectively, been shown to attenuate attentional regulation of working memory or the efficiency of perceptual decision-making. Results from studies applying TMS to investigate abstract rule learning or cognitive decision-making also implicate various medial and anterior regions of the PFC in these functions. Specifically, in tasks that require the integration of different aspects of choice options (e.g., amount, probability, and time point of reward), a disruption of the right dorsolateral PFC with 1-Hz rTMS was shown to increase the risky behavior of choosing low-probability options that were associated with large reward (Knoch et al., 2006). Other studies of intertemporal choices showed that low-frequency 1-Hz rTMS applied to either the left (Figner et al., 2010) or the right (Essex et al., 2012) dorsolateral PFC (dlPFC) disrupted the integration of information about the time point of reward and increased choices for immediate smaller rewards over larger but delayed rewards. As for investigations about the roles of dlPFC in maintaining mental representations (models) of complex decisions, a more recent study (Smittenaar et al., 2013) applied inhibitory continuous theta burst transcranial magnetic stimulation (cTBS) during a probabilistic 2-stage Markov decision task (Daw et al., 2011). In this case, a transient disruption of the right dlPFC reduced model-based choice behavior, which relied on representing the probabilistic structure of the task. Inhibition of the left dlPFC only affected model-based behavior in individuals with low working memory capacity (Smittenaar et al., 2013). Taken together, existing findings show that the lateral PFC is implicated in effects of the amount, time point, or probability of reward on value-based learning and decision-making. However, questions about the potential causal roles of the lateral PFC in integrating information about sequential transitions between successive choice states are still pretty much open.

Adaptive behavior in daily life often requires complex value-based learning and decision-making across successive steps. Specifically, it demands the ability to acquire and represent contingent relations between sequential actions and outcomes. Consider the example of a person who had just moved to a new city: the overall goal to get home from work as quickly as possible by the public transportation does not specify which sequence of actions would better serve the goal (e.g., taking the underground Line 1 and change to Line 3, or taking the Line 2 and then switch to bus). In such situations, the individual needs to learn the transitions between the successive transfer points as well as the concurrent and temporally lagged action–outcome associations through trial and error (e.g., the ride on Line 1 takes 5 min vs. the ride with Line 2 needs 9 min; however, at the next transfer point, there will be a 15-min lag until Line 3 arrives, but only a 5-min wait for the bus). Crucially, the individual needs to integrate information about the action–outcome contingences across sequential states (e.g., one action leads to more waiting time than the other at the next transfer point), in order to choose the optimal route. An earlier study by Tanaka et al. (2004) investigated such sequential decision processes using a deterministic 3-stage Markov decision task. The property of a Markov decision task is that an action (or decision) at a given state not only determines the outcome on that current state but also determines the specific transition into the subsequent state. Learning the sequential state-dependent contingencies between choices and outcomes across multiple states is necessary to perform such tasks successfully. Specifically, blood-oxygen-level dependent (BOLD) activity in the left dlPFC was associated with the behavior of taking actions associated with minor negative consequences (e.g., small monetary losses) in earlier states in order to gain a better net outcome (e.g., a larger reward) at a later state in the sequence (Tanaka et al., 2004). In light of these results, we recently studied the effects of aging on learning complex sequential state transitions using a variant of the 3-stage Markov task (Eppinger et al., 2015; cf. Tanaka et al., 2004). Our results showed that aging is associated with performance decrement, particularly in situations that necessitate the learning of cross-state action-outcome contingencies for optimizing long-term outcomes. The observed behavioral impairment was associated with under-recruitments of various regions of the PFC in older adults, including areas such as left rostrolateral, right dorsolateral, and right medial PFC. Most relevant for the current study, in younger adults the BOLD activity in left dlPFC (Talairach coordinates $x = -41$, $y = 25$, $z = 22$) was associated with shifts of the choice behavior towards taking the optimal sequential actions during the course of learning. Specifically, the BOLD activity in this region was high in the beginning of learning, but decreased after younger adults had acquired the transition structure of the task, as reflected in clear changes in their choice behavior (Eppinger et al., 2015). Together, these results suggest that the left dlPFC is involved in learning complex sequential relations. Relatedly, previous evidence also suggests that the left dlPFC is associated with processing higher-order relations (i.e., relations of relations), beyond simple first-order associations between stimulus features (Bunge et al., 2009).

To summarize, the correlational findings from fMRI studies in a young adult sample (Tanaka et al., 2004) and from an age-comparative sample (Eppinger et al., 2015) indicate that the left dlPFC is associated with acquiring complex sequential transitions as well as with aging-related impairments in this function. However, the direct effects of this region on sequential decision-making still remain to be established. Therefore, in this study we set out to investigate the link between the left dlPFC and the process of integrating information about sequential state transitions in young adults by applying rTMS to transiently inhibit the left dlPFC.

Materials and methods

Participants

Thirty-five young male participants were recruited through advertisements on the campus of Technische Universität (TU) Dresden. Our focus on male participants was motivated by results from previous studies showing that menstrual cycle related hormonal changes in females could affect cortical excitability (Inghilleri et al., 2004; Smith et al., 1999). All participants were screened for rTMS eligibility (e.g., history of psychiatric illness or neurological disorder) before study participation (Rossi et al., 2011). Furthermore, handedness is known to be associated with individual differences in the lateralization of hemispheric activations during some cognitive and motor tasks (see Willems et al., 2014, for review), including the lateralization of the dorsal frontoparietal network (Petit et al., 2015). Thus, prior to study participation we explicitly asked the participants about their handedness and included only right-handed individuals. Four participants had to be excluded from the study because of difficulties in reliably discerning the motor threshold ($n = 1$), unusual transient facial muscle contractions during stimulation ($n = 1$) or because they were not able to participate in the second session due to personal reasons ($n = 2$). Thus, the effective sample consisted of 31 healthy young male participants (mean age = 23.8 years, age range: 19–32 years, $SD = 2.5$ years). Since ten participants did not perform the task above the chance level, analyses of rTMS effects on choice behavior were focused on the non-chance performers ($n = 21$), who were in either of the two treatment groups (10 vertex-starters and 11 dlPFC-starters) in a within-subject cross-over design (see below for more details about screening chance performers).

Appraising the sample size, we conducted power calculations based on effect sizes estimated from prior studies. To this end, we first conducted a literature search with the following five criteria: the studies investigated effects of (1) 1-Hz inhibitory rTMS stimulation over (2) the dlPFC or nearby prefrontal brain regions on (3) relevant cognitive functions (including decision-making, cognitive control, working memory) and (4) had a sample size of at least 10 subjects as well as (5) reported the necessary information for estimating effect sizes (i.e., *F*-statistics and relevant degrees of freedom). Following this procedure, we identified 8 studies with 13 reported effects in total for our analyses (i.e., Bahlmann et al., 2015; Baumgartner et al., 2011; Brüne et al., 2012; Hoffman et al., 2010; Kalbe et al., 2010; Knoch et al., 2006; Philiastides et al., 2011; Weigand et al., 2013). Specifically, effect sizes (partial eta-squared, i.e., η^2_{partial}) of these studies were estimated based on the *F*-

statistics and the degrees of freedom of the associated effects (Lakens, 2013; Maxwell et al., 1981). The estimated $\eta^2_{partial}$ of these prior studies ranged from 0.19 to 0.39, with a mean of 0.27. To stay conservative in estimating the sample size, we calculated the power for detecting effects at the minimum and mean values of the $\eta^2_{partial}$ estimated from prior studies. Using G*Power (Version 3.1.9.2), the estimated values of $\eta^2_{partial}$ were first converted into generic effect sizes, resulting in $f = 0.48$ ($\eta^2_{partial} = 0.19$) and $f = 0.61$ ($\eta^2_{partial} = 0.27$). Subsequently, we conducted an a-priori power analysis using these two levels of effect sizes for the repeated measures design, with two repeated measurements, a significance level of $\alpha = 0.05$ (two-tailed), the statistical power $(1\text{-}\beta) = 0.95$ and an $r = 0.5$ for the correlation between the repeated measurements. The results of the power analysis suggest that a total sample of 18 or 12 participants would be required for detecting the rTMS x task condition interaction effects at the level of $\eta^2_{partial} = 0.19$ (minimum) or 0.27 (mean), respectively. For detecting the rTMS main effect, the corresponding effect sizes would require 16 or 11 participants, respectively. Thus, the total effective sample size of our study ($n = 21$; 10 vertex-starters and 11 dlPFC-starters) has sufficient power in detecting small to mean level rTMS effect sizes as observed in prior findings. The ethical committee of TU Dresden approved the study. All participants gave written informed consent for their participations. The participants received 8 Euro per hour for study participation as well as the additional amount of money (on average about a total of 15 Euro) they earned during the main experimental task as a bonus for their performance.

Off-line rTMS protocol and within-subject cross-over design

In the experimental condition, we applied a 20-min train (1200 pulses) of low-frequency 1-Hz rTMS over the left dlPFC to transiently suppress neural activity in young adults. The target stimulation site of the left dlPFC was selected based on results from our previous fMRI study (Eppinger et al., 2015), as this was the region associated with young adults' earlier and more distinct behavioral choice shifts towards taking the optimal sequential actions during learning (the Talairach coordinates $x = -41$, $y = 25$, $z = 22$ reflect the peak of the BOLD activity). To navigate the TMS coil to this target brain region, we created a 3-D brain model from the participants' individual T1-scans using the PowerMAG View Navigation software (Mag & More, Munich, Germany). The individual brain model was co-registered with the participant's head and the TMS coil in our lab using specific position points tracked by an infrared camera (Polaris Vicra; Northern Digital Inc., Ontario, Canada). This allowed an online navigation, which made it possible to position the TMS coil on the participant's head with an exact reference to the individual brain model and thereby more precise stimulations of the target location. In the control condition, as commonly done, we applied the stimulation into the interhemispheric cleft of the vertex (cf. Davis et al., 2013; Duecker et al., 2013). A recent concurrent TMS/fMRI study showed that a short set of single-pulse suprathreshold TMS stimulations at 120% of motor threshold applied over the vertex during the resting state did not increase or interfere with ongoing BOLD activity at the stimulated site, in support of the use of vertex stimulation as a control stimulation (Jung et al., 2016). Furthermore, Jung et al. (2016) showed that vertex stimulation was associated with deactivations in various distributed brain regions, including the anterior cingulate cortex, inferior parietal lobe and precuneus, partly overlapping with the default mode network. Stimulations applied over vertex, however, did not affect the functional connectivity in this network. Juxtaposing the results of Jung et al. (2016) about vertex stimulation together with other findings about brain stimulation effects on the default mode network during the resting state (e.g., Eldaief et al., 2011) and anti-associations between default mode and task-related networks (Anticevic et al., 2012) suggest that applying TMS over the vertex for protocols aiming at inhibiting task-related activity would be a conservative, rather than liberal, control stimulation. The target location of the vertex was set to the position of the Cz electrode of the 10–20 system (see Fig. 1A for the stimulation sites). In our case, stimulation intensity was set at 100% of the participant's individual motor threshold (see below for details of assessing individual motor threshold).

To compare effects of left dlPFC and vertex stimulations, we used a within-subject cross-over design (Fig. 1B): for half of the participants (the dlPFC-starters) the stimulations were applied over the left dlPFC in the first session and over the vertex in the second session, whereas the remaining half of the participants (the vertex-starters) received the stimulations in the reversed order. Across participants the two sessions were, on average, one week apart (mean interval = 7 days, SD = 0.4 day). The stimulations were applied off-line for 20 min, with the main experimental task been performed immediately after the stimulations in each of the two sessions.

As cortical excitability varies across and within individuals (Ziemann and Hallett, 2007), we determined the stimulation intensity individually for each participant in relation to the cortical excitability as indicated by the motor threshold (MT) in each session. The MT represents the minimum amount of electrical energy needed to induce motor movement, which is visible in the contralateral limb or body when TMS is applied over the motor cortex (McConnell et al., 2001). The MT is also recommended as a measure of cortical TMS susceptibility when TMS is applied outside of the motor regions (Kaminski et al., 2011). Specifically, the MT is commonly defined as the lowest intensity capable to elicit motor evoked potentials (MEPs) greater than 50 μV peak-to-peak amplitude in at least half of consecutive trials (five out of ten in the current study) in resting or activated (slightly contracted) target muscles (Kobayashi and Pascual-Leone, 2003). We followed the Rossini-Rothwell procedure (Rossini et al., 1994; Rothwell et al., 1999; cf. Tranulis et al., 2006) to determine the individual MT for each participant. We recorded MEPs on the first dorsal interosseous (FDI) muscle of the right hand that were elicited by a single pulse of TMS over the left motor cortex (M1). Specifically, an initial TMS pulse was delivered at a point located approximately 5 cm lateral and 2 cm anterior from the position of the vertex (i.e., midpoint between nasion-to-inion and left-to-right preauricular) at an intermediate level of 50% maximum stimulator output (MSO). If no MEP could be observed then the so-called “motor hotspot” for the FDI muscle was searched for systematically in an approximate 2 cm radius around this initial point. If necessary (i.e., if there was still no measurable motor response), the MSO was increased by 2% and the procedure was repeated. Following successful identification of a cortical point with reliable MEPs, stimulation intensity was systematically lowered by 2% until 5 out of 10 pulses produced MEPs with a 50 μV peak-to-peak amplitude. The percentage of MSO at this intensity was then considered the participant's MT. The assessments of the MT and the administering of rTMS were done by using a MagPro X100 Magstim Rapid Magnetic Stimulator (Magstim, Winchester, MA) and a MagStim figure-eight MCF-B65 butterfly coil (75-mm diameter double-circle). The single pulses of TMS were applied approximately every 10 s (±1 s) with a varying interval between pulses (±1 s) to avoid priming effects, which could affect the MEP signals. The signals were recorded using Ambu Neuroline 700 surface electrodes (Ambu GmbH, Bad Nauheim, Germany), a BrainVision ExG MR amplifier and BrainVision Recorder software (Brain Products GmbH, Munich, Germany).

For applying the stimulations, the coil was held tangential to the participant's head, with the handle pointing upright over the vertex or upright but diagonally in an inferior-to-posterior orientation over the left dlPFC. To keep the participants in relaxed mode, they could watch an episode of *The Big Bang Theory*, a popular American sitcom, during the 20 minutes of rTMS. Two episodes from the series were selected, one for each of the two sessions. All participants watched the same episode in the respective session. After the stimulation, participants immediately performed the 3-stage Markov decision task. During and after stimulation, none of the participants reported any adverse effects of the rTMS stimulation (e.g., headaches, scalp or neck pain).

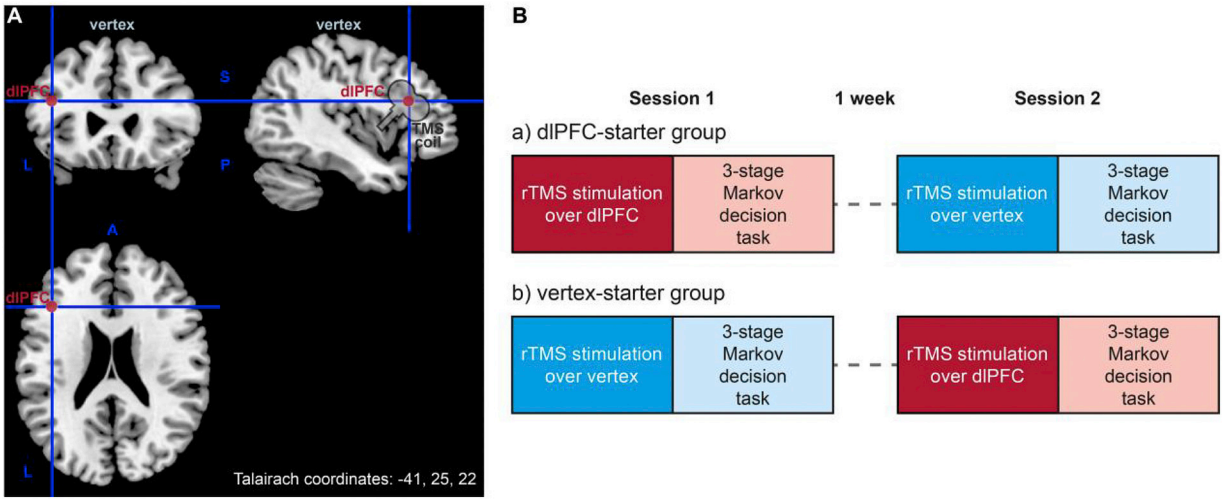

Fig. 1. rTMS stimulation sites (A) and the within-subject cross-over design (B).

Experimental task and procedure

We used a variant of the 3-stage Markov decision task (Fig. 2A) as in our previous fMRI study (Eppinger et al., 2015), with minor modifications in trial duration, trial number, and reward magnitude. The modifications of trial duration and numbers were undertaken to adapt the task for the expected duration of rTMS after-stimulation effect. The task was programmed using the EPrime 2.0 software (PST Inc., Pittsburgh, PA). Task presentation and data collection were conducted on a standard ASUS S56C laptop computer, with a 15.6-inch LED-screen. In a Markov decision task, an action at a specific choice state not only determines the outcome associated with the current state, but also the course of transitions to subsequent states (Tanaka et al., 2004). At each of the three states (s1, s2, s3), the participants were instructed to make a two-alternative forced choice between two possible action options by pressing one of two response keys after the state-specific visual stimulus was presented. The task consisted of two conditions: In the *immediate reward* condition, if the participant learned to take the optimal sequence of action (shown in green in Fig. 2A), a small gain of 5 cents was rewarded at all three states. Contrarily, the other suboptimal sequence of action (shown in red in Fig. 2A) consistently resulted in a loss of 5 cents at all three states. In this condition, the concurrent action–outcome associations at each of the three states was informative for the cumulative gains or losses across the series of sequential decisions. In the *delayed reward condition*, the optimal sequence of actions (shown in green in Fig. 2A), was associated with small losses of 5 cents at the first two states (s1, s2) and a big reward of 25 cents at the third state (s3), resulting in a net gain of 15 cents; whereas the suboptimal sequence of actions (shown in red in Fig. 2A) was associated with small gains of 5 cents in the two initial states, but a big loss of 25 cents at the third state, resulting in a net loss of 15 cents. As such, the lagged, cross-state action-outcome associations were important for performance in the delayed condition. The expected cumulative amount of rewards along the optimal sequence through a cycle of three states was the same for the immediate (+0.05 × 3) and the delayed (−0.05, −0.05, +0.25) conditions. The immediate and delayed reward conditions were manipulated block-wise, with one practice and three experimental blocks for each of the two conditions. The participants were instructed to maximize overall gains and minimize losses.

Each trial started with the presentation of a fixation cross for a fixed interval of 0.5 s. In case participants missed a response in the allowed 1-s response time window, the words “too slow” appeared on the screen and the trial was repeated. After the participant responded, the feedback for the current state as well as the amount of rewards accumulated thus far were presented for 1.5 s (Fig. 2B). The timeout trials were discarded from the analyses (<3.5% in the vertex-starter group and <4.5% in the dlPFC-starter group).

The task started with the practice phase, during which participants were first introduced to all possible combinations of stimuli, actions and outcomes to familiarize them with the two learning conditions. Subsequently, they performed one practice block for each of the two learning

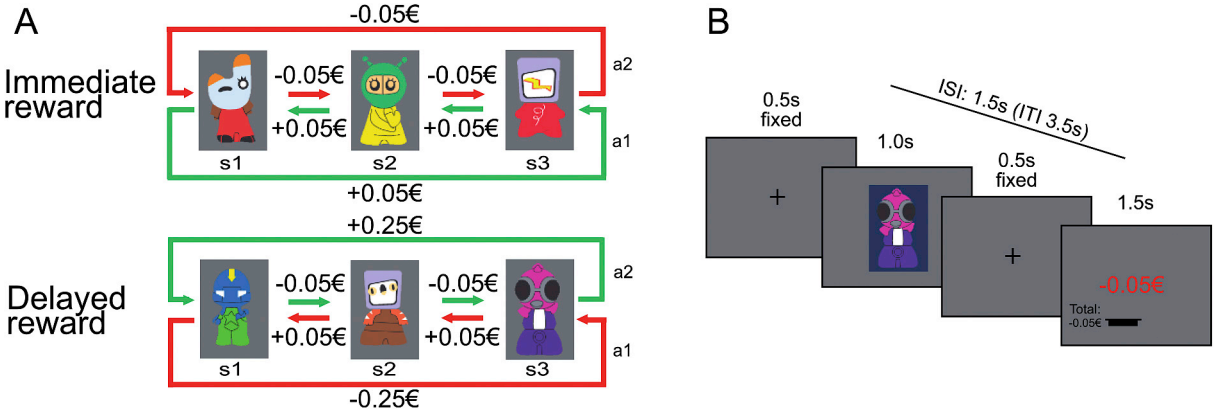

Fig. 2. Schematic figure of the 3-state Markov decision task with two conditions, showing the state transition structure (A) and trial procedure (B).

conditions. The practice blocks were terminated once the participants reached a mean level of 60% in accurately choosing actions along the optimal action sequence or completed a maximum number of practice trials (36 and 72 trials were allowed for immediate and delayed condition, respectively). In each of the two sessions, during the experimental phase the participants completed 6 experimental blocks (3 blocks for each learning condition). In designing the task, colorful abstract figures were created using free software that was available online (gogoscrazybones.com) and processed in Photoshop for presentation purpose. Each of the colorful abstract figures denotes a specific state in a given block of a condition. Each practice and experimental block included a unique set of 3 abstract figures to indicate the three states of a sequence. Altogether 24 colored abstract figures were shown in each of the two experimental sessions. A block entailed a total of 36 trials (i.e., 12 cycles through the 3-state sequence), which resulted in 108 trials for the immediate and delayed reward condition each. The participants were randomly assigned to a counter-balanced ordering of the blocks.

Measures of cognitive and motivational traits

Besides the main experimental task, individual differences in motivation relevant traits were assessed by the commonly used *BIS/BAS scales* (Carver and White, 1994), which reflect individual differences in the sensitivity to reward (the BAS scale) or punishment (the BIS scale). Furthermore, we also included several psychometric tests to assess basic cognitive abilities (i.e., reasoning, perceptual speed, memory and verbal knowledge, cf. Li et al., 2004). These measures were assessed to evaluate between-group comparability and to serve as covariates if necessary. Logical reasoning ability was assessed with the *Wiener Matrizen-Test 2* (WMT-2). Test scores of the WMT-2 correlate highly (r = 0.74) with the popular Standard Progressive Matrices (Raven et al., 2000); thus, it is a suitable alternative test for assessing individual differences in analogical reasoning (Formann et al., 2011). Cognitive speed was assessed by the *Identical Pictures Test* (Lindenberger et al., 1993). Verbal knowledge was assessed by a German version of the *Spot-a-Word Test*, a lexical decision task used to assess verbal ability in adults (cf. Baddeley et al., 1993; Lindenberger et al., 1993). We also assessed memory span using the *Digit-Span Test* from the Wechsler Adult Intelligence Scale (WAIS-IV; Petermann and Wechsler, 2012).

Study procedure

In Session 1, the participants first completed a demographic questionnaire, the BIS/BAS scales, the Identical Pictures Test and Spot-a-Word Test. After the psychometric tests, the individual motor threshold (MT) was determined, followed by the practice phase of the Markov decision task. Young adults then received the 20-min rTMS stimulation over either the left dlPFC or vertex, depending on whether they were in the group of the dlPFC-starters or the vertex-starters. Immediately following the rTMS stimulation, they completed the Markov decision task, which took on average 13 min. Before leaving the lab, they also performed the Digit-Span test. The procedure for Session 2 proceeded likewise, except that participants completed the WMT-2 reasoning test at the beginning of the session instead of the questionnaires and covariates collected in Session 1.

Overview of data screening and analyses

Statistical analyses were performed using Matlab (Mathworks Inc., Natick, MA) and R packages (version 0.98.932) in RStudio (www.rstudio.com). We first identified participants whose performance accuracy (the proportion of choosing options that are in the optimal action sequence) in the delayed reward condition was indeed above chance level by using the Chi-square contingency test. Those participants whose numbers of correct and incorrect trials in the delayed reward condition across both sessions differed significantly ($p < 0.05$) from the expected chance distribution (i.e., equal distribution of correct and incorrect trials) were classified as non-chance performers, whereas those participants whose numbers of correct and incorrect trials did not differ significantly from the expected chance distribution were classified as chance performers. Altogether, we identified five chance performers in each of the two treatment groups (vertex- and dlPFC-starters).

Next, control analyses comparing sample characteristics across the subsamples were conducted first using analyses of variance (ANOVA) on measures of cognitive and motivational traits as well as motor thresholds (see results summarized in Table 1). These analyses allowed us to first check for potential confounds before analyzing effects of rTMS stimulations on decision performance. When relevant, multiple comparison tests were performed using the Tukey-Kramer correction (Dunnett, 1980). Regarding motivational traits, the three subsamples (vertex-starters, dlPFC-starters and chance performers) did not differ in behavioral inhibition or approach (BIS/BAS) scores. Similarly, motor thresholds also did not differ between the groups (all p-values > 0.23). As for basic cognitive abilities, the groups also did not differ with respect to their scores on the Digit-Span, Identical-Pictures and Spot-a-Word Tests (all p-values > 0.37), besides chance performers' lower score on the WMT-2 test assessing reasoning ability ($p = 0.05$). Given the chance performers' lower reasoning ability, which might confound the effects of inhibitory rTMS on sequential decision-making and their floor-level (chance) performance in the delayed reward condition that is indistinguishable from the performance of an older-adult comparison sample (see supplementary information for details), we thus restricted the analyses of rTMS effects only to the non-chance performers.

In each session, learning across blocks was computed based on mean accuracy and reaction times (RTs) for each participant across six consecutive equally sized trial bins (two bins per block) for the two experimental conditions. Furthermore, drift diffusion models are frequently used to decompose performance in forced two-alternative

Table 1
Comparisons of sample characteristics across subsamples of younger adults.

Demographic & psychometric measures	Non-chance vertex-starters (n = 10) mean (SD)	Non-chance dlPFC-starters (n = 11) mean (SD)	Chance-performers (n = 10) mean (SD)	Group effect p-value	Group effect effect size
Age	23.7 (1.1)	23.0 (2.1)	24.9 (3.4)	$p = 0.21$	$\eta2 = 0.12$
WMT-2	15.9 (2.0)	15.2 (1.6)	13.7 (2.2)	$p = 0.05$	$\eta2 = 0.24$
Digit-Span (S1)	15.6 (3.5)	15.8 (4.1)	17.0 (1.9)	$p = 0.61$	$\eta2 = 0.04$
Digit-Span (S2)	16.8 (4.0)	16.8 (4.6)	17.8 (2.6)	$p = 0.80$	$\eta2 = 0.02$
Identical Pictures	36.4 (3.7)	35.6 (5.0)	34.6 (3.5)	$p = 0.63$	$\eta2 = 0.03$
Spot-a-Word	20.6 (6.6)	20.4 (5.7)	17.1 (6.0)	$p = 0.37$	$\eta2 = 0.07$
BIS	17.0 (2.6)	18.6 (2.1)	18.7 (2.8)	$p = 0.23$	$\eta2 = 0.11$
BAS	13.0 (1.4)	13.2 (1.7)	13.5 (1.6)	$p = 0.72$	$\eta2 = 0.02$
MT (S1)	49.6 (6.3)	49.2 (5.6)	48.3 (5.5)	$p = 0.88$	$\eta2 = 0.01$
MT (S2)	51.1 (4.4)	50.2 (5.9)	48.2 (6.2)	$p = 0.50$	$\eta2 = 0.05$

choice tasks into underlying processes of decision-making (Forstmann et al., 2016; Pedersen et al., 2016). Specifically, the drift diffusion model captures decision-making as a process of continuous sampling of noisy decision evidence until a decision boundary in favor of one of the choice options is reached. Noise in the decision process could encompass noise in the perceptual representations of choice options as well as in the memory representations of choice–outcome associations. According to the model, the distributions of choice accuracy and RTs across trials depend on a number of parameters, three of which are central in most decision processes. The drift rate (v) models the efficiency with which decision evidence could be integrated across trials to approach the decision boundaries: high drift rates reflect more efficient evidence integration. The boundary separation parameter (a), which adjusts the speed–accuracy tradeoff, indicates the amount of evidence needed until a decision criterion is reached: wider decision boundaries would reflect more cautious but slower decisions. The non-decision time parameter (*Ter*) captures the time taken by sensory encoding and motor processes. Of note, low-frequency rTMS applied over the posterior left dlPFC during perceptual decision-making has previously been shown to attenuate the efficiency of sensory information integration that was captured by one of the drift diffusion parameters (Philiastides et al., 2011). In the context of the Markov decision task here, at each decision state there is the possibility to transition into one of two possible subsequent states, depending on the participant's choice at the given state. Thus, in addition to using decision accuracy and RTs as performance indices, we also applied the EZ-diffusion model (Wagenmakers et al., 2007) to our data to further characterize potential effects of rTMS stimulation on different aspects of the decision process that are reflected in the parameters of the model. Specifically, we applied the model to each non-chance performer's data from the immediate and delayed reward condition separately for the two simulation sessions, in order to estimate the three drift diffusion parameters described above. In the EZ-diffusion model, the parameters are estimated based on the individual's decision accuracy as well as the mean and variance of RTs of the correct responses. In the context of the Markov decision task, these three parameters presumably reflect the efficiency of integrating information (v) about the sequential transitions, stringency of the decision criterion (a), and sensorimotor processing time (*Ter*). Before applying the model to our data, RT distributions associated with choices made in each of the three states were inspected separately for the immediate and delayed reward condition. All distributions can be characterized as ex-Gaussian, which is expected for RT distributions. Furthermore, key characteristics of the distributions (mean, variance, kurtosis and skewness) did not differ between the three choice states within conditions.

All statistical analyses were conducted using linear mixed effects models with maximum-likelihood (ML) estimation and subjects as random intercepts. The intraclass correlation coefficient (ICC) is the recommended measure of effect sizes for models involving random effects (Maxwell et al., 1981). To ease the interpretation about the percentage of variance associated with a given effect, we also provide squared ICC values for this information in the results section (Fern and Monroe, 1996). Given that the group factor (dlPFC-starters vs. vertex-starters) in the cross-over design fully determined which brain region was stimulated in each of the two sessions (i.e., left dlPFC or vertex stimulation), group and session effects were not separable when analyzed in a repeated measures design. Linear mixed effects models can differentiate these effects and flexibly account for degrees of freedom and model covariances at the within- (i.e., session, condition, learning bin) and between-subject (i.e., treatment group) levels (see Garrett et al., 2015; Thurm et al., 2016 for similar approaches). We conducted the linear mixed effects models using the *lme* function from the *nlme* package in R (Pinheiro et al., 2015). Multiple-comparisons were carried out using pairwise t-tests (two-tailed) with Holm-correction for multiple testing (Holm, 1979). Specifically, in our analyses the between-subject factor *Group* refers to the distinction between the dlPFC-starter and the vertex-starter group. As for within-subject effects, the following four factors were used for the analyses of decision accuracy (proportion of choosing options in the optimal action sequence) and RT: the factor *Treatment* (indicating vertex or dlPFC stimulation), *Session* (referring to the two testing sessions, Session 1 (S1) and Session 2 (S2)), *Condition* (i.e., the immediate or delayed reward condition), and *Bin* (depicting the course of learning, from Bin 1 to Bin 6). As the parameters of the diffusion model were estimated based on data from all blocks within a given learning condition, statistical analyses involving diffusion parameters included three of the above within-subject factors, but not the *Bin* factor. The normality of the distributions of all models' residuals was examined using the Shapiro-Wilk-test (W-statistic) as well as by visual inspection using Q-Q-plots. In case of normality violations, we performed permutation tests using *permmodels* from the *predictmeans* package in R. No substantial differences in the direction or magnitude of the observed effects were found in any of the permutated models. Lastly, Pearson's correlation analyses were conducted to assess the cross-session correlations between the efficiency of integrating information about sequential transitions at Session 1 and making crucial state transitions at Session 2.

Results

We analyzed effects of rTMS on performance in both sessions in the two groups of young non-chance performers with respect to decision accuracy, RT and the three drift diffusion parameters (v, a, and *Ter*) derived from the EZ-diffusion model.

rTMS effects on accuracy

In terms of within-subject effects, results of the linear mixed effects model for decision accuracy revealed significant main effects of Condition, $F_{(1,436)} = 148.2$, $p < 0.0001$, $ICC = 0.50$ (25.0%[1]), Session, $F_{(1,436)} = 160.2$, $p < 0.0001$, $ICC = 0.52$ (27.0%), Bin, $F_{(5,436)} = 75.4$, $p < 0.0001$, $ICC = 0.68$ (46.2%) and Treatment, $F_{(1,436)} = 5.7$; $p = 0.02$, $ICC = 0.11$ (1.2%). Furthermore, we also observed significant 2-way Treatment x Condition, $F_{(1,436)} = 4.5$, $p = 0.03$, $ICC = 0.10$ (1.0%), Session x Condition, $F_{(1,436)} = 47.5$, $p < 0.0001$, $ICC = 0.31$ (9.6%), Session x Bin, $F_{(5,436)} = 3.7$, $p = 0.003$, $ICC = 0.20$ (4.0%) interactions and a significant 3-way Treatment x Session x Condition interaction, $F_{(1,436)} = 8.5$, $p = 0.004$, $ICC = 0.14$ (2.0%). The main effect of Bin was well in line with our previous findings (Eppinger et al., 2015), showing clear learning effects across the trial bins. Similarly, the main effect of Condition was as expected and replicated previous findings: overall, performance in the immediate reward condition was better than in the delayed reward condition (Eppinger et al., 2015; Tanaka et al., 2004).

To further investigate the 3-way interaction indicating possible treatment group related effects, we conducted analyses with Group (vertex-starters vs. dlPFC-starters) as the between-subject factor and Condition (immediate vs. delayed reward) as within-subject factor separately for the two sessions. In Session 1, the results revealed a significant main effect of Condition, $F_{(1,229)} = 77.5$, $p < 0.0001$, $ICC = 0.50$ (25.0%), no significant main effect of Group ($p = 0.12$), but a significant Group x Condition interaction, $F_{(1,229)} = 4.7$, $p = 0.03$, $ICC = 0.14$ (2.0%). Specifically, these results indicated that in Session 1 participants under dlPFC stimulation (the dlPFC-starters) performed significantly worse compared to participants under vertex stimulation (the vertex-starters) in the delayed reward condition ($p = 0.004$), whereas there was no difference between these two groups in the immediate reward condition ($p = 0.46$). Results from Session 2 again revealed a main effect of Condition, $F_{(1,229)} = 11.5$, $p = 0.0008$, $ICC = 0.22$ (4.8%), showing better performance in the immediate than the delayed reward condition; however, there was no main effect of Group ($p = 0.09$) nor a Group x Condition interaction ($p = 0.46$). Together, these results (shown in Fig. 3)

[1] This value is the squared *ICC*, which indicates the percentage of variance associated with the effect.

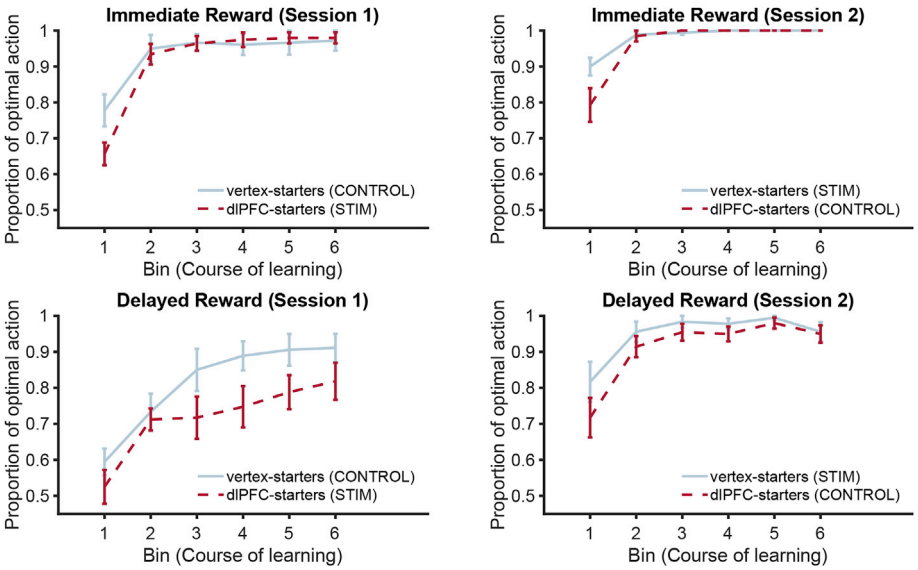

Fig. 3. Effects of 1-Hz rTMS on the proportion of optimal action by condition and session (error bars indicate one standard error). The dlPFC-starters received the stimulation (STIM) over the left dlPFC in Session 1 and the control stimulation (CONTROL) over the vertex in Session 2. The vertex-starters received the control stimulation (CONTROL) in Session 1 and the stimulation (STIM) over the left dlPFC in Session 2. Key interaction effects in these results show that performance accuracy in the immediate reward condition was not affected by rTMS, whereas rTMS over the left dlPFC significantly attenuated performance in the delayed reward condition, particularly in Session 1.

indicate that without prior experience with the task, suppressing left dlPFC activity with rTMS specifically impaired sequential decision-making that involved delayed rewards: the average learning curve of dlPFC-starters reached a lower asymptote. In Session 2, the performance was overall higher, revealing the Session main effect. However, the performance of the vertex-starters who were on dlPFC inhibitory stimulation in this session was not surpassed by the dlPFC-starters, who were off the inhibitory stimulation in this case. Together, this pattern of results indicates that for vertex-starters, despite disrupted left dlPFC activity in Session 2 when they received dlPFC stimulation, their more efficient learning and higher performance level in Session 1 buffered their performance in the later session, without showing impairments. Note, however, as performance accuracy in Session 2 approached ceiling in both groups, results based on RT and diffusion parameters that take into account both accuracy and RT reported below could shed further light on this finding.

rTMS effects on RTs

Regarding within-subject effects, results of the linear mixed effects model for reaction times (shown in Fig. 4) revealed significant main effects of Treatment, $F_{(1,436)} = 9.4$, $p = 0.002$, $ICC = 0.15$ (2.3%), Session, $F_{(1,436)} = 271.5$, $p < 0.0001$, $ICC = 0.62$ (38.4%), Condition, $F_{(1,436)} = 68.2$, $p < 0.0001$, $ICC = 0.37$ (13.7%) and Bin, $F_{(5,436)} = 37.2$, $p < 0.0001$, $ICC = 0.55$ (30.3%). We also observed significant 2-way Treatment x Session, $F_{(1,436)} = 4.0$, $p = 0.046$, $ICC = 0.10$ (1.0%), Session x Condition, $F_{(1,436)} = 20.8$, $p < 0.0001$, $ICC = 0.21$ (4.4%), Session x Bin, $F_{(5,436)} = 4.3$, $p = 0.001$, $ICC = 0.22$ (4.8%), Condition x Bin,

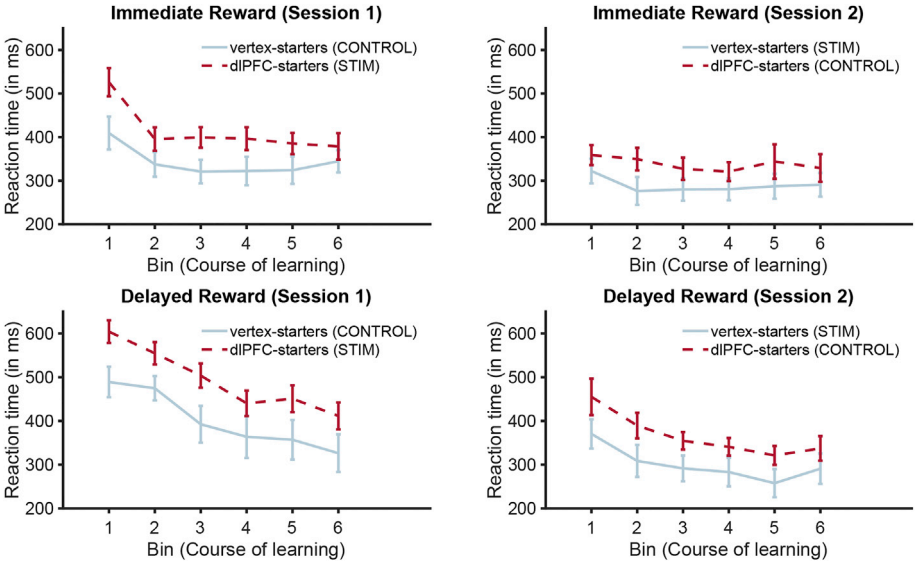

Fig. 4. Effects of 1-Hz rTMS on reaction times by condition and session in young non-chance performers (error bars indicate one standard error). The dlPFC-starters received the stimulation (STIM) over the left dlPFC in Session 1 and the control stimulation (CONTROL) over the vertex in Session 2. The vertex-starters received the control stimulation (CONTROL) in Session 1 and the stimulation (STIM) over the left dlPFC in Session 2. Key interaction effects in these results show that rTMS over the left dlPFC significantly increased RTs in both conditions, with the effects being larger in Session 1. Learning significantly reduced RTs also in Session 2, but only in the delayed condition.

$F_{(5,436)} = 7.1$, $p < 0.0001$, $ICC = 0.27$ (7.3%) interactions and a significant 3-way Session x Condition x Bin interaction, $F_{(5,436)} = 2.6$, $p = 0.02$, $ICC = 0.17$ (2.9%). Similar to the accuracy data, the main effects of Bin and Condition were as expected based on prior results (Eppinger et al., 2015; Tanaka et al., 2004). The 3-way interaction involving these two factors and the Session factor indicated that decision speed still improved across bins in the second session, but only in the delayed not in the immediate condition. Differing from the results for accuracy, no 3-way interaction involving the Treatment factor was observed. This indicates that the dlPFC-starters consistently took longer times than the vertex-starters in making their decisions in both sessions, albeit they being under the control stimulation in Session 2.

rTMS effects on parameter estimates derived from the diffusion model

Drift rate (v). In terms of within-subject effects, results of the linear mixed effects model for drift rate (shown in Fig. 5) revealed significant main effects of Session, $F_{(1,56)} = 72.0$, $p < 0.0001$, $ICC = 0.75$ (56.3%) and Condition, $F_{(1,56)} = 56.4$, $p < 0.0001$, $ICC = 0.71$ (50.4%). Moreover, a significant 2-way Session x Condition interaction, $F_{(1,56)} = 13.1$, $p = 0.001$, $ICC = 0.43$ (18.5%) was observed, reflecting a reduced effect of condition in Session 2. Follow-up post-hoc analyses showed that the expected effect of learning condition was observed in Session 1 ($t_{(39.2)} = 5.3$, $p < 0.0001$) but was only marginally significant in Session 2 ($t_{(35.6)} = 2.0$, $p = 0.053$). Furthermore, the results also yielded a significant 2-way Treatment x Session interaction, $F_{(1,56)} = 8.7$, $p = 0.005$, $ICC = 0.37$ (13.7%). However, no significant 3-way interaction involving the Condition factor was observed. Thus, to further investigate this 2-way interaction, post hoc analyses were carried out separately for each session with data averaged across conditions using t-tests to compare means of the two starter groups. This analysis revealed that the drift rate was significantly lower in the dlPFC-starters irrespective of task conditions in Session 1 ($t_{(34.0)} = 2.1$, $p = 0.04$) as well as in Session 2 ($t_{(38.8)} = 3.3$, $p = 0.002$). These results suggest that rTMS stimulation over the left dlPFC impaired the efficiency of integrating information about sequential transitions across decision states. Furthermore, although in general the information integration rate of the dlPFC-starters increased in Session 2 when they were under the control stimulation, the increased integration efficiency was still lower that of the vertex-starters who received the inhibitory stimulation in this session, but initially had the opportunity to perform the task with undisturbed dlPFC function in the first session.

Boundary separation (a). Results of the linear mixed effects model for boundary separation revealed a significant main effect of Session, $F_{(1,56)} = 19.7$, $p < 0.0001$, $ICC = 0.51$ (26.0%) and Condition, $F_{(1,56)} = 12.4$, $p = 0.0009$, $ICC = 0.43$ (18.5%). No significant main effect of Treatment ($p = 0.35$) or any interactions (all p-values > 0.15) were observed. These results indicate that although the response criterion was more stringent (larger boundary separation) in Session 2 and in the immediate reward condition, it was not affected by rTMS stimulation.

Non-decision time (Ter). Results of the linear mixed effects model for non-decision time revealed a significant main effect of Condition, $F_{(1,56)} = 12.1$, $p = 0.001$, $ICC = 0.42$ (17.6%), with values of the *Ter* parameter being larger in the immediate than in the delayed condition. A significant Session x Condition interaction, $F_{(1,56)} = 10.8$, $p = 0.002$, $ICC = 0.40$ (16.0%) showed that the condition effect on non-decision time was only present in Session 1. Otherwise, no main effects of Treatment ($p = 0.41$), Session ($p = 0.34$) or other interactions (all p-values > 0.34) were observed. These results indicate that rTMS stimulation did not affect the speed of the non-decision (e.g., sensorimotor) aspect of the processing.

Analyses of cross-session correlations

To further explore whether the positive carry-over effect from Session 1 to Session 2 in the vertex-starters, who had the opportunity to perform the task in Session 1 with undisturbed left dlPFC, may reflect their benefits of being able to better integrate information about sequential transitions during initial learning in Session 1, we conducted additional cross-session correlational analyses. Specifically, we expected that better information integration about sequential transitions might allow them to establish a better representation of crucial state transitions. To this end, for each vertex-starter we calculated the proportion of successful transitions from state 2 (s2) to state 3 (s3) in the delayed condition, which was the crucial transition to obtain the delayed large reward. Identical analyses were also conducted for the dlPFC-starters for comparison. One dlPFC-starter's proportion of making the crucial state transition was more than 5 standard deviations below the group mean (SD = 5.28) and was thus excluded from the correlational analyses. Individual differences in successfully making the crucial state 2-to-3 transition correlated significantly between Session 1 and Session 2 across participants in both treatment groups ($r = 0.56$, $p = 0.01$), indicating test-retest rank-order reliability in the decision performance assessed with the task. We further

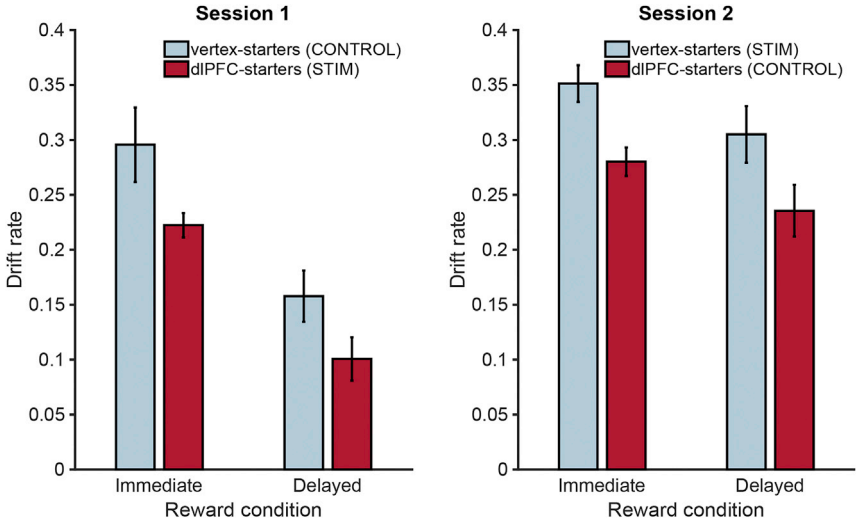

Fig. 5. Effects of 1-Hz rTMS on drift rate by condition and session in young non-chance performers (error bars indicate one standard error). The dlPFC-starters received the stimulation (STIM) over the left dlPFC in Session 1 and the control stimulation (CONTROL) over the vertex in Session 2. The vertex-starters received the control stimulation (CONTROL) in Session 1 and the stimulation (STIM) over the left dlPFC in Session 2. Key interaction effects in these results show that drift rate (efficiency of information integration) was significantly higher in the immediate than in the delayed condition, with the effect being larger in Session 1. rTMS significantly attenuated the drift rates in both conditions, with dlPFC-starters showing lower drift rate across both sessions.

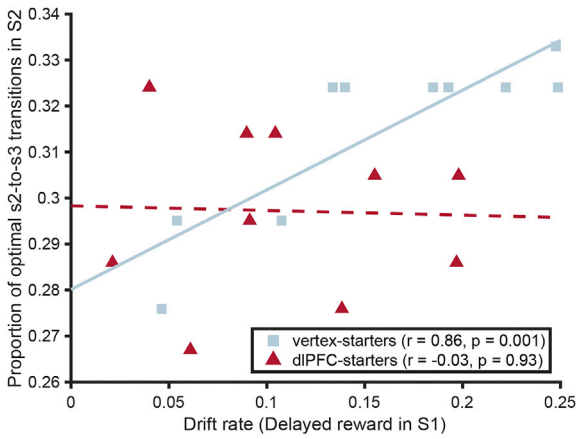

Fig. 6. Cross-session correlations between drift rate estimated from data in the first session (S1) and the proportion of succeeding in making the crucial state 2-to-3 transition during Session 2 (S2) in the delayed reward condition separated for vertex-starters and dlPFC-starters. Using the Fisher r-to-z transformation to test the difference between these two correlations yielded a significant effect ($z = 2.56$, $p = 0.01$).

explored the specific relationship between the effect of rTMS on the efficiency of information integration as reflected in the drift rate parameter in Session 1 and successful state 2-to-3 transition in Session 2 separately for the two treatment groups. As shown in Fig. 6, drift rates in Session 1 correlate positively with the proportion of making the crucial state 2-to-3 transition in Session 2 in the vertex-starters ($r = 0.86$, $p = 0.001$) but not in the dlPFC-starters ($r = -0.03$, $p = 0.93$). Together, this pattern of results indicates that the 3-stage Markov decision task has good rank-order reliability and that inhibitory 1-Hz rTMS stimulation over the left dlPFC during initial learning attenuated performance potential and the associated individual differences.

In light of earlier results showing lateral PFC's role in supporting relational integration processes during higher-order analogical reasoning (e.g., Bunge et al., 2005; Christoff et al., 2001), we also checked whether the observed cross-session correlation between drift rate and making crucial sequential transition would remain significant after controlling for individual differences in analogical reasoning ability. In line with previous findings, across both the vertex- and dlPFC-starters reasoning ability as assessed by the WMT-2 in our data correlated moderately ($r = 0.48$, $p = 0.03$) with the behavior of making the crucial state 2-to-3 transitions in the delayed condition in Session 1. Importantly, however, in vertex-starters partialling out individual differences in reasoning ability or the overall performance of choosing the optimal actions in Session 2 only minimally attenuated the cross-session correlation between drift rate in Session 1 and the performance of making the crucial transition observed in Session 2 ($r = 0.81$, $p = 0.008$ and $r = 0.76$, $p = 0.02$ after controlling for reasoning ability or the overall performance accuracy, respectively). Taken together, these results indicate that in vertex-starters the positive carry-over effects between sessions could be attributed to a positive relation between more efficient information integration about sequential transitions during initial learning in Session 1 and a great success in making the crucial state 2-to-3 transitions in Session 2.

Discussions

Although increasingly more findings from fMRI, lesion and TMS studies have lend support for the lateral PFC's involvements in value-based learning and decision-making (for a recent review see Dixon and Christoff, 2014), its role in value-based sequential decision-making that requires the acquisition of complex sequential transitions and cross-temporal contingencies is not yet well established. To fill this gap, we used a within-subject cross-over design to investigate the effects of an off-line inhibitory rTMS protocol over young male adults' left dlPFC on performance in a 3-stage deterministic Markov decision task. Other than effects on the sequential choice behavior and decision time, we also examined potential impacts of rTMS on drift diffusion parameters estimated using the EZ-diffusion model (Wagenmakers et al., 2007). Extending previous correlational findings from fMRI (Tanaka et al., 2004) and our own age-comparative study (Eppinger et al., 2015), results from the current study provide further support for the role of the left dlPFC in complex value-based learning and shed lights on the potential link between dlPFC and the efficiency of information integration across decision states during sequential decision-making. The main findings are discussed in details below.

Inhibitory stimulation applied over the left dlPFC attenuated the behavior of choosing options in the optimal action sequence, particularly in situations where the acquisition of sequential transitions across decision states is crucial for performing optimally in the long run. If only based on performance accuracy, at first sight it may seem that the reduced rTMS effect on decision accuracy in Session 2 could, in part, reflect a ceiling effect. However, subsequent analyses using a drift diffusion model that considers both accuracy and RTs suggest more principled influences of rTMS on acquiring representations of complex sequential transitions. *First*, the disadvantage of having to learn the task with inhibited left dlPFC during Session 1 persisted into Session 2, which was clearly evident in comparing the RTs of the dlPFC-starters with those of the vertex-starters. In both sessions, the dlPFC-starters took longer to make their decisions. *Second*, results regarding the drift rate showed a similar pattern: dlPFC-starters consistently showed smaller drift rates than the vertex-starters in both sessions, indicating that the integration of information about sequential transitions was impaired by inhibitory rTMS during initial learning in the first session and the negative consequence persisted into the subsequent session. Moreover, the effect of rTMS on process parameters derived from the diffusion model was only specific to the information integration process. Although the parameters reflecting the stringency of the response criterion (a) and non-decision time (*Ter*) were sensitive to the time point of reward and the extend of learning as reflected, respectively, in the observed effects of learning condition and session, inhibitory rTMS over the left dlPFC did not affect either of these two parameters. *Third*, results from analyzing the cross-session relation between the efficiency of information integration and optimal choice behavior showed that, indeed, individual differences in drift rate during initial learning in Session 1 and the proportion of successfully making the crucial state transition for gaining the delayed reward in Session 2 was positively correlated in the vertex-starters. Those vertex-starters who were more efficient in integrating information across decision states during initial learning were also more successful in making the crucial transition in Session 2 to obtain the delayed larger rewards, even though their left dlPFC was inhibited in Session 2. Although alternative sets of stimuli were used and counterbalanced for the two sessions, the main sequential transition structures for the immediate and delayed conditions remained the same across sessions. In a standard one-session fMRI study without treatment cross-overs, we have previously shown that, during the course of learning within one session, BOLD activity in the left dlPFC was high during initial learning; however, BOLD activity decreased after the participants had acquired the sequence of state transitions (Eppinger et al., 2015). Extrapolating this pattern of prior results to interpret the current cross-session findings, the vertex-starters, who could learn more about the optimal choice sequence in the delayed condition with *intact* left dlPFC in Session 1, could generalize their learned representation of this sequential transition to Session 2. Once the representation of the sequential transition is learned, choice behavior is less depended on the dlPFC in Session 2, thus the performance of the vertex-starters in Session 2 while under inhibitory rTMS could still be buffered by the initial learning in Session 1. Relatedly, although in Session 2 the learning of new stimulus–outcome pairs at each state would be required, such learning mainly involves simple concurrent within-state association but not cross-state integration, given that the general task transition structure has been acquired in Session 1. The

learning of stimulus–outcome associations within each state relies relatively more on striatal than frontal activities (cf. Daw et al., 2011; O'Doherty et al., 2003). Thus, inhibiting the left dlPFC of vertex-starters in the second session had relatively little influence on different measures of choice behavior.

Taken together, the cross-over design of 1-Hz rTMS in our study allowed us to investigate the roles of the left dlPFC in affecting complex value-based learning in which sequential state transitions involving lagged action-outcome contingencies are important for decisions. Unlike the dlPFC-starters, the vertex-starters were able to perform the task with uninterrupted left dlPFC function initially in the first session. This allowed them to more efficiently integrate information across decision states to acquire the sequential transition structure, which resulted in a higher performance level. Once they have learned the state transition structure, the decision performance becomes less dependent on the left dlPFC; thus, their performance and further learning during the second session was not impaired, even though their left dlPFC function was suppressed in this later session. These effects cannot be attributed to potential confounds in terms of between-group differences in basic cognitive or motivational traits, as both the vertex-starter and dlPFC-starter groups were comparable on a varieties of control variables that were also assessed.

Our findings also extend previous studies on PFC's roles in value-based learning and decision-making. In line with results from previous TMS studies on intertemporal choices (Essex et al., 2012; Figner et al., 2010) and model-based vs. model-free learning (Smittenaar et al., 2013), our results implicate dlPFC's roles in complex value-based learning and decision-making. Previous studies using intertemporal choice tasks focused mainly on lateral PFC's function in integrating information about the time point of rewards (Essex et al., 2012; Figner et al., 2010); whereas studies on model-based vs. model-free learning focused on lateral PFC's role in representing probability-based decision structures (Daw et al., 2011; Smittenaar et al., 2013). Having a different focus and by utilizing the deterministic 3-stage Markov task, our findings shed further evidence on left dlPFC's roles in integrating complex sequential relations and temporal contingencies across decision states as well as the potential of such learning. Our findings are also in line with the results from a recent study, which showed that the anatomical integrity of the left prefrontal cortex, along with other regions (bilateral hippocampus), is associated with the individual's ability of making sequential inference in a category reversal learning task (FitzGerald et al., 2017).

Furthermore, our results also lend support to evidence suggesting a rostro-caudal axis of PFC's functional divisions. Accumulating evidence indicates that the anterior and mid-dorsolateral PFC are involved in the learning of complex rules and processing relational information (see Badre & D'Esposito, 2009, for review). Whereas previous studies on complex rule learning and relational integration applied tasks that tap analogical reasoning (e.g., Bunge et al., 2009, 2005; Christoff et al., 2001), our findings extend lateral PFC's roles to situations involving the integration of sequential relations across value-based decision states. In our data, we also found that individual differences in reasoning ability as measured by the WMT-2 test correlated moderately with the performance success in making the crucial state 2-to-3 transition in the delayed reward condition. Of note, however, after controlling for individual differences in reasoning ability, the efficiency of integrating information about the sequential transitions during initial learning as reflected in the drift rate parameter assessed in Session 1 still uniquely predicted the success of making optimal choices at the crucial transition in Session 2, specifically in individuals who had the opportunity to acquire the state transitions during initial learning without interrupted left dlPFC function. Furthermore, our results are also in line with earlier findings suggesting that whereas the right lateral PFC seems to be primarily sensitive to capacity demands of information processing imposed by the complexity of stimulus features, the left lateral PFC modulates the integration of higher-order relational information (Bunge et al., 2009). The rostro-caudal division of the frontal lobe functions (i.e., the rostro-lateral regions being more involved as the complexity of relational integration increases) may even extend further into the orbitofrontal cortex. Specifically, a recent study showed that the orbitofrontal cortex is implicated in the acquisition and representation of state transitions between 16 states in a complex learning task (Schuck et al., 2016).

Other than clear negative aging-related differences in sequential decisions that could in part be attributed to an under-recruitment of regions in dlPFC (e.g., Eppinger et al., 2015), individual differences in young adults are also substantial. In our data screening analyses, about one third of the young participants performed at chance level and their rather low performance level was not distinguishable from that of an older-adult comparison sample (see supplementary information). Although the young chance performers did not differ significantly from the non-chance performers with respect to any of the control measures of cognitive and motivational traits, they scored lower for reasoning ability. This is in line with previous evidence suggesting that the lateral PFC supports relational integration during higher-order analogical reasoning tests (e.g., Bunge et al., 2005; Christoff et al., 2001). Furthermore, individual differences in working memory updating might be another factor that could contribute to individual differences in the effects of rTMS on sequential decision-making. It has been shown that working memory operation span modulated the balance between model-based and model-free value-based learning (e.g., Eppinger et al., 2013) as well as the effects of rTMS stimulation (e.g., Smittenaar et al., 2013) in a 2-stage Markov decision task.

Taken together, given the multifaceted roles of dlPFC in value-based learning and sequential decision-making that require integrations across complex state transitions as well as the clear age-related impairment in such learning in older adults (Eppinger et al., 2015), it would be important for future studies to explore other stimulation methods, such as excitatory 10-Hz rTMS (e.g., Strafella et al., 2001) or transcranial direct current stimulation methods (e.g., Filmer et al., 2017; see Filmer et al., 2014; Passow et al., 2017 for reviews) over similar regions to explore possibilities for enhancing the acquisition and representation of complex sequential transitions in older adults. To this end, effort needs to be devoted towards adapting stimulation protocols for older adults, since the responses to brain stimulations have been shown to vary as a function of age and other factors. More generally, effects of brain stimulations are state-dependent (e.g., Learmonth et al., 2015), which could result in substantial interindividual variability in intervention outcomes (e.g., Eldaief et al., 2011). Furthermore, interindividual differences in baseline task performance (e.g., Jones and Berryhill, 2012; Tseng et al., 2012), working memory functions (e.g., Smittenaar et al., 2013), and functional connectivity in the default mode network (Eldaief et al., 2011) may also modulate individual differences in the effects of TMS on task-related performance and brain functions. Thus, future research needs to invest considerable attention to assess baseline performance with broad ranges of relevant covariates and brain activities in the default mode network, in order to more closely delineate individual and age differences in the mechanisms underlying effects of TMS on complex value-based learning and decision-making.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.neuroimage.2017.11.057.

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