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Absence of associative motor learning and impaired time perception in a rare case of complete cerebellar agenesis

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ABSTRACT

Primary cerebellar agenesis (PCA), a brain disease where the cerebellum does not develop, is an extremely rare congenital disease with only eleven living cases reported thus far. Studies of the PCA case will thus provide valuable insights into the necessity of cerebellar development for controlling and modulating cognitive functions of the brain. In this follow-up study, we further investigated the performance of associative learning and time perception of a 26-year-old female complete PCA case. We assessed whether delayed eyeblink conditioning (EBC), which represents prototypical associative motor learning function of the cerebellum, could be partially compensated by the extracerebellar brain regions in complete absence of the cerebellum. We also assessed whether the cerebellum, a critical brain region for millisecond-range interval timing, is essential for perception of the second-range time interval. Twelve neurotypical age-matched individuals were used as controls. We found that although the complete PCA patient had only mild to moderate motor deficits, she was unable to perform the delayed EBC even after 1-week of extensive training. Additionally, the PCA patient also performed poorly during time reproduction experiments in which she overproduced the millisecond-range time intervals, while underproduced the second-range time intervals. The PCA patient also failed to perform the temporal eyeblink conditioning with a 5 s fixed interval as the conditioned stimulus. These results indicate that the cerebellum is indispensable for associative motor learning and involved in timing of sub-second intervals, as well as in the perception of second-range intervals.

1. Introduction

Primary cerebellar agenesis (PCA) is an extremely rare disease with a high mortality rate (Arrigoni et al., 2015; Ashraf et al., 2016; Yu et al., 2015). PCA results from severe developmental disorder and typically presents with motor and mental deficits, epilepsy, hydrocephaly and other functional or anatomical brain impairments (Tavano et al., 2007; Yu et al., 2015). Most PCA patients die at an early age, with only eleven living cases having been reported since 1982 (Arrigoni et al., 2015; Ashraf et al., 2016; Mormina et al., 2016; Tavano et al., 2007; Yu et al., 2015). Therefore, it is paramount to study cerebellum-dependent motor and non-motor functions, and how extracerebellar brain regions compensate in this rare medical disorder. Yu et al. (Yu et al., 2015) previously reported on a recent PCA case involving a 24 years old female. They demonstrated a complete absence of the cerebellum by using both computerized (CT) and functional magnetic resonance imaging (fMRI) scans. Surprisingly, although the cerebellum was completely absent, the patient presented only mild to moderate motor deficits and mild mental impairment. This corresponded with previously reported cases, which also showed only mild deficits or even normal motor functions in congenital PCA patients (Ashraf et al., 2016; Sener and Jinkins, 1993). This phenomenon is consistent with the notion that the extracerebellar motor system has the capacity to compensate for cerebellar motor functions under the conditions of total or subtotal loss of the cerebellum (Ashraf et al., 2016; Tavano et al., 2007; Yu et al., 2015). In this study, we addressed whether and to what extent the cerebellum-dependent cognitive functions, such as associative learning and time perception, could be compensated for by the extracerebellar brain regions under complete congenital cerebellum absence.

Cerebellar-dependent associative motor learning has been widely investigated during the past forty years (Hasan et al., 2013; Shinkman et al., 1996; Thompson, 2005; Wu et al., 2017; Yeo and Hardiman,

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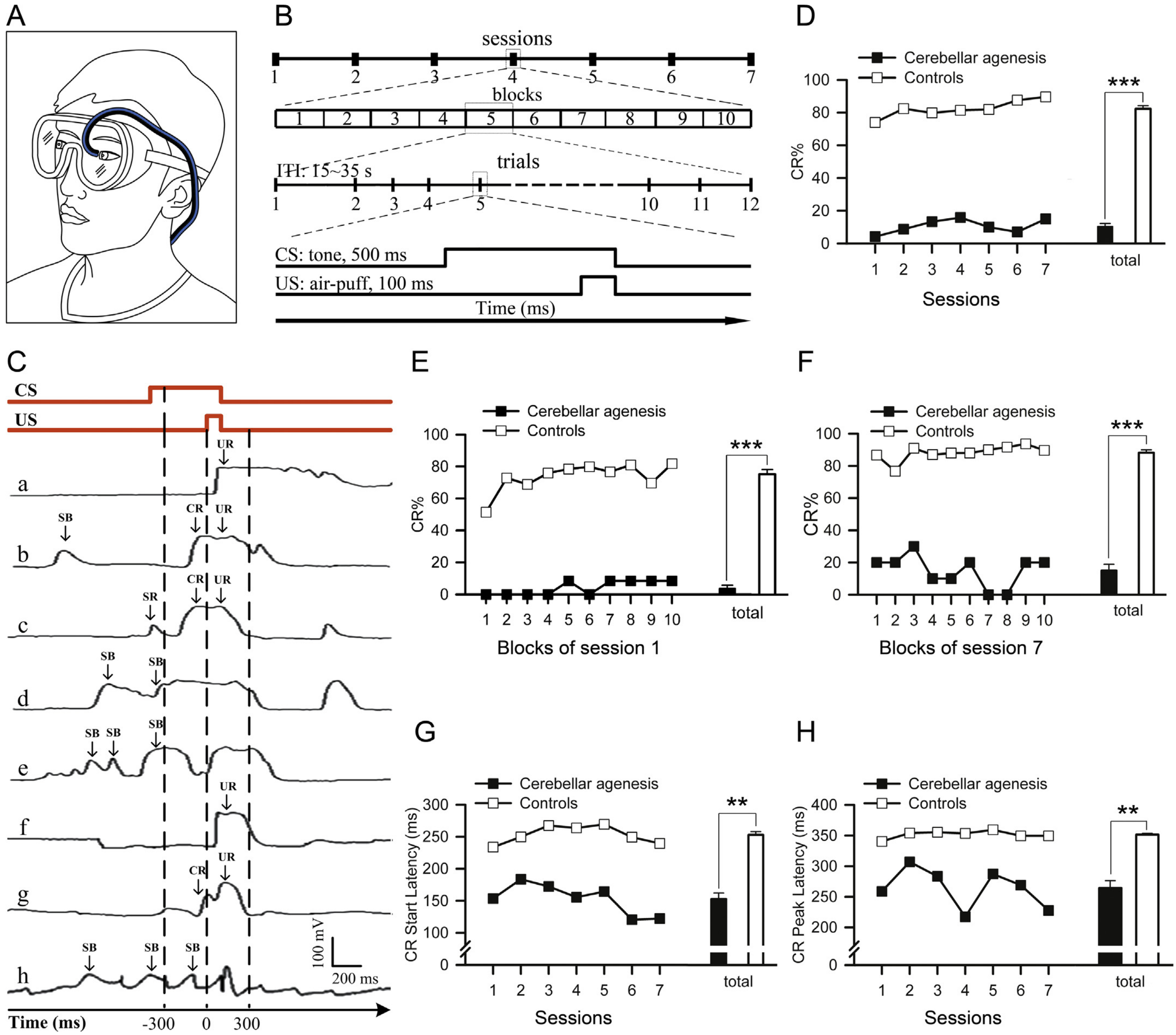

Fig. 1. The behavioural paradigm and results of delay eye-blink conditioning (DEC). (A) The infrared emitter/detector and an air-puff delivery pipe were permanently secured together on the goggle's left lens with dental acrylic. (B) Training paradigm and temporal relationship between the conditioned stimulus (CS) and unconditioned stimulus (US). (C) Representative examples of various response types encountered during the course of DEC. Panel a to e are behavioural recordings of controls and panel f to h are of the PCA patient. Panel a and f are examples of a UR alone that occurred after the US onset. Panel b shows a CR with longer latency. Panel c shows a CR with short-latency and a startle response (SR, this data were not analyzed in this study). The CR and UR emerged successively and merged after learning. The CR usually had equal or smaller amplitude than the UR, which was the maximal blink and had more stable waveform than the CR. Panel d, e and h are examples of bad trials in which spontaneous eye-blink response (SB) emerged before the onset of the CS and contaminated the CRs. Trials like this had been excluded from analyses. (D) Percentage of conditioned responses (CR%) in the PCA patient and controls ($n = 12$, $df = 11$) across the 7 daily sessions. (E) and (F) CR% of each block on session 1 (E) and session 7 (F). (G) The CR start latency and (H) CR peak latency of the PCA patient and controls during the 7 sessions. Right histograms in Fig. D to H represent total mean values of the corresponding dynamic value in the left line graphs. Data of bars are represented as mean ± standard error of the mean (SEM). Error bars indicate the SEM. $^{**}P < 0.01$, $^{***}P < 0.001$ vs control.

1992), The classical eyeblink conditioning (EBC) is an ideal assay for studying associative motor learning, in which subjects learn to blink to a conditioned stimulus (CS, e.g., a tone or a light) just before an unconditioned stimulus (US, e.g., an air puff or a periorbital electrical stimulation). The prototypical EBC model is characterized by instantaneous, automatic and adaptive behavior, with accumulative lesion studies demonstrating that EBC is dependent on the cerebellum, an essential organ mainly engaged in motor control (McCormick and Thompson, 1984; Yeo and Hesslow, 1998). It has been proposed that the specific tissue organization inside cerebellum enables it to correlate the temporally dissociated signals (e.g., CS and US) between very short intervals, eventually forming specific associative memory (Steinmetz, 2000). However, given the limitations of classical lesion studies in which cerebellar lesions are usually incomplete, thereby remaining cerebellar structures are able to compensate, evidence from these studies about whether the cerebellum provides a unique and indispensable contribution to associative motor learning remains insufficient. Therefore, additional research is required to further address such questions. The opportunity to study a congenital, but not acquired case of complete cerebellar absence in a living adult, will provide invaluable