Cerebellar-dependent associative learning is impaired in very preterm born children and young adults

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Background and aims:

Preterm birth incorporates not only an increased risk for focal cerebellar lesions, but also for impaired cerebellar development. Cerebellar developmental disorders likely contribute to motor and cognitive abnormalities.

Experimental evidence of cerebellar dysfunction, however, is sparse.

Methods:

Standard delay eyeblink conditioning was performed, a simple form of associative learning that is highly dependent on the integrity of the cerebellum (see Fig. 1).

Focal lesions were excluded based on structural magnetic resonance imaging.

Two cohorts of former preterm infants (< 32 weeks gestational age (GA)) were investigated and compared to an equal number of sex- and age-matched term born controls (see Table 1):

Children	Preterm subjects (n=32)	Controls (n=32)
age (mean, range, years)	5,8 (5,0 - 6,6)	5,8 (5,0 - 6,7)
sex (m/f)	16/16	16/16
GA (MW, range, weeks)	28,0 (23,7 - 31,7)	39,4 (37,0 - 41,6)
BW (MW, range, g)	1047 (540 - 1670)	3397 (2630 - 4060)
Adults	Preterm subjects (n=20)	Controls (n=20)
age (mean, range, years)	19,4 (18,1 - 24,5)	19,9 (18,5 - 23,5)
sex (m/f)	10/10	10/10
GA (MW, range, weeks)	28,9 (23,2 - 32,0)	39,4 (37,0 - 41,0)
BW (MW, range, g)	1219 (650 - 1970)	3471 (2540 - 4300)

A subgroup of children (12 preterm, 12 controls) were retested.

Results:

Very preterm born adults acquired significantly less conditioned responses compared to matched control subjects and their learning rate was slower (group effect, $P < 0.001$, block by group interaction, $P = 0.02$; analysis of variance with repeated measures), (see Fig. 2).

Preterm preschool children acquired less conditioned responses than matched controls in the subgroups of children tested twice (group effect, $P = 0.02$), (see Fig. 2).

Preterm children did not show the same increase in conditioned response size between sessions as controls (session by group interaction, $P = 0.002$), (see Fig. 3).

Conclusion:

Preterm birth impedes function of the cerebellum even in the absence of focal cerebellar lesions

Prematurity results in long-term detrimental effects on the integrity of the cerebellum

Fig.1: Experimental set-up (a) and delay eyeblink conditioning paradigm (b,c). The number of trials in the unpaired, acquisition and extinction phase is shown for the adult and the children's group, respectively.

CS= conditioned stimulus (that is a tone of 540 ms duration indicated in blue); US= unconditioned stimulus (that is, an airpuff of 100 ms duration, indicated in grey).

Fig.2: Acquisition and extinction of conditioned eyeblinks in adults (a). Mean percentage conditioned response (CR) incidence and standard error (SE) are shown in preterm born adults (○) and control adults (●). The first ten blocks are acquisition blocks, the last three blocks extinction blocks. Each block corresponds to ten trials.

Eyeblink conditioning in characteristic preterm and control adult (b). EMG-data of the orbicularis muscle are shown in the 100-paired CS-US acquisition trials with the first trial at the top and the last trial at the bottom. The first solid vertical line indicates the onset of the CS (the tone), the second solid vertical line indicates the onset of the US (the air puff). EMG responses occurring in the time interval of 150 ms after CS onset (indicated by the hatched line) and US onset were identified as CRs. EMG: electromyography; CS = conditioned stimulus; US = unconditioned stimulus; CR = conditioned response

Fig.3: Acquisition and extinction of conditioned eyeblinks in children (a). Mean percentage conditioned response (CR) incidence and standard error (SE) are shown in preterm children (○) and control children (●). Data is shown in (a) the groups of all children (n = 32 per group) and (b) in the subgroups tested twice (session 1 and session 2; n = 12 per group). The first ten blocks are acquisition blocks. Ext = extinction block. Each block corresponds to ten trials.