Aberrant functional connectivity between motor and language networks in rolandic epilepsy

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KEYWORDS
Benign rolandic epilepsy of childhood with centro temporal spikes; Language impairment; Resting-state functional MRI

Summary
Introduction: Rolandic epilepsy (RE) is an idiopathic focal childhood epilepsy with a well-established neuropsychological profile of language impairment. The aim of this study is to provide a functional correlate that links rolandic (sensorimotor) pathology to language problems using functional MRI.

Materials and methods: Twenty-three children with RE (8–14 years old) and 21 matched controls underwent extensive language assessment (Clinical Evaluation of Language Fundamentals). fMRI was performed at rest and using word generation, reading, and finger tapping paradigms. Since no activation group differences were found, regions of interest (ROIs) were defined at pooled (patients and controls combined) activation maxima and in contralateral homotopic cortex, and used to assess language lateralization as well as for a resting-state connectivity analysis. Furthermore, the association between connection strength and language performance was investigated.

Results: Reduced language performance was found in the children with RE. Bilateral activation was found for both language tasks with some predominance of the left hemisphere in both
groups. Compared to controls, patient connectivity was decreased between the left sensorimotor area and right inferior frontal gyrus ($p < 0.01$). For this connection, lower connectivity was associated with lower language scores in the patient group ($r = 0.49$, $p = 0.02$), but not in the controls.

**Conclusion:** Language laterality analysis revealed bilateral language representation in the age range under study (8–14 years). As a consequence, the connection of reduced functional connectivity we found represents an impaired interplay between motor and language networks, and aberrant functional connectivity associated with poorer language performance. These findings provide a first neuronal correlate in terms of aberrant resting-state functional connectivity for language impairment in RE.

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**Introduction**

Rolandi episyl mal (RE) is an idiopathic focal epilepsy of childhood with typical onset at 7–10 years of age (Panayiotopoulos et al., 2008). It is also known as benign epilepsy of childhood with centro-temporal spikes (BECTS), which reflects both its mild seizure semiology and the location of the seizure onset zone on EEG (sensorimotor cortex, i.e. Rolandic area). Seizures include hemispheric spasms and speech arrest and occur mostly at night (Hughes, 2010; Nayar and Beausart, 1998). Furthermore, spontaneous remission of seizures is typically observed during adolescence (Hughes, 2010; Loiseau and Duché, 1989; Massa et al., 2001).

Classically, RE is thought to occur in children of normal intellect without neuropsychological problems (Loiseau and Duché, 1989). In recent years, however, evidence has accumulated that serious co-morbidities may occur, such as behavioral problems, oromotor deficits and language impairment (Kanemura and Alhara, 2009; Monjaufe et al., 2005; Nicolai et al., 2006; Northcott et al., 2007; Overvliet et al., 2010; Panayiotopoulos et al., 2008). This has put the assumed benign nature of RE under debate (Nicolai et al., 2006; Vinayan et al., 2005; Völlki-Kernstock et al., 2009; Weglage et al., 1997). This includes a discussion on whether it is clinically desirable and/or beneficial to treat RE, for example by means of anti-epileptic drugs (Hughes, 2010).

Especially language impairment is increasingly recognized and extensively described with respect to neurocognitive profile (Monjaufe et al., 2005; Northcott et al., 2005; Nicolai et al., 2006; Papavasiliou et al., 2005). Interestingly, in RE a significant correlation has been demonstrated between problems in motor and language problems in normal development, which suggests a common cerebral origin (Gündüz et al., 1999; Overvliet et al., 2011a).

Based on EEG, measures have been developed for cognitive impairment risk in RE (Massa et al., 2001), and associations have been described between the nature of the language impairments and the laterality of the epileptiform abnormalities (Lillywhite et al., 2009; Riva et al., 2007). However, these studies remain inconclusive with respect to the underlying cerebral mechanism. Its unveiling is highly desirable as even though the cognitive deficits in RE are typically deemed reversible (Panayiotopoulos et al., 2008), it has been suggested that in specific cases they may persist after seizure remission (Kanemura and Alhara, 2009; Monjaufe et al., 2011). Moreover, insight into the pathophysiological mechanism is relevant for the interpretation of delays in scholar development and to motivate treatment strategies.

The language problems, but also the inattention and impulsivity seen in RE, suggest dysfunction in circuits distant from the Rolandic area (Massa et al., 2001). In a study of frontal lobe epilepsy in children, it was suggested that abnormalities distal to the seizure onset zone might be involved in the spread of seizure activity or the development of secondary epilepsyogenic zones (Widjaja et al., 2011). These suggestions prompt research employing connectivity analysis to explore potentially aberrant connections in children with RE that could explain the language impairment.

The aim of this study is to investigate whether in RE aberrant functional connectivity can be found between motor and language areas, which might link the location of the epileptic focus (sensorimotor cortex) to the language impairment. Task fMRI is used to identify language and motor networks. Since atypical language lateralization on fMRI has been reported in pediatric epilepsy before (Liegeois et al., 2004; Yuan et al., 2006), the laterality of language activation is also investigated. Resting-state fMRI (rs-fMRI) is employed to determine the functional connectivity within and between the identified functional networks. Language performance is assessed using the Clinical Evaluation of Language Fundamentals (CELF) test for children and the association between connection strength and language performance is studied.

**Materials and methods**

**Selection criteria**

Children with RE were selected at the specialized epilepsy referral center Kempenhaeghe based on clinical criteria concerning electroencephalography (EEG) and seizure semiology as described in the literature (Berroya et al., 2005; Panayiotopoulos et al., 2008). EEG criteria include the presence of spike and slow wave complexes occurring as individual paroxysms or in repetitive clusters with a maximum in mid-temporal and/or central electrodes and with a temporal–frontal dipole field. Additional independent central, mid-temporal, parietal or occipital spike-wave foci in the same or other hemisphere were allowed. To exclude severe cases (Landau-Kleffner syndrome (LKS) or LKS-like),
interictal epileptiform activity was required to be present <85% of the time during non-REM sleep. With respect to seizure semiology, seizures with anarthria, hemichonia involving the face and/or unilateral extremities, or secondarily generalized seizures were considered. In case of poorly observed nocturnal seizures, post ictal signs of a generalized seizure or confirmation of post ictal hemiparesis were sufficient for inclusion in case of otherwise typical EEG.

Study population

Twenty-three children (7 girls) with RE were selected. The age at epilepsy onset (mean ± SD) was 7.5 ± 2.1 and the age at testing 11.4 ± 2.0 years (range: 8–14 years). Nineteen children were right handed, 3 were left handed and 1 child was ambidextrous. As a control group, 21 healthy controls were selected (10 girls, age 10.5 ± 1.6 years, range 8–14 years, 20 right handed and 1 left handed). The age distributions of both groups were comparable (t-test, p = 0.11).

As part of their diagnostic workup, the children with RE underwent the Wechsler Intelligence Score for Children, 3rd edition and all had a full-scale IQ >70. None of the healthy controls had a history of dyslexia, learning disorders or psychiatric disorders, nor attended special education. Children were excluded if they had dental braces (MRI quality) or were somewhat afraid in the scanner.

A board certified neuroradiologist specialized in epilepsy (PH, 20 years of experience) reviewed all scans and found no structural abnormalities.

The study was approved by the boards of the medical ethical committees of both participating institutions. All parents (or guardians) gave written informed consent prior to study participation.

Language assessment

To assess language performance, the Clinical Evaluation of Language Fundamentals, 4th edition (CELF-4), Dutch version was used (Paslawski, 2005; Semel et al., 2010). The CELF-4 is considered the gold standard for language assessment in children and provides several age-corrected metrics. Among these is the core language score, which was assessed in all subjects and is a general language measure that may serve as a screening measure for language impairment. More specific sub metrics were only assessed in the patients to assess which specific language aspects may be impaired. Differences in language performance of the patients with respect to the controls and norm values were assessed using Student’s t-tests employing a significance level of p < 0.05.

MRI acquisition and preprocessing

Structural MRI

Structural MRI was performed for anatomical reference at 3.0 Tesla (Philips Achieva system; Philips Medical System, Best, the Netherlands) using an 8-element receive-only head coil. A T1-weighted scan was acquired using the following settings: voxel size 1 mm × 1 mm × 1 mm, field of view (FOV) 240 mm × 240 mm × 150 mm, flip angle 8°, 3D fast spoiled gradient echo sequence, echo time/repetition time/inversion time (TE/TR/TI) 3.8/8.3/1022 ms and acquisition time 8 min. Additionally a T2-weighted scan was acquired (TE/TR 80/3000 ms), as well as a fluid attention inversion recovery (FLAIR) sequence (TE/TR/TI 125/1100/2800 ms) at voxel size 0.45 mm × 0.45 mm × 5.5 mm, FOV 230 mm × 230 mm × 143 mm, and flip angle 90°.

Functional MRI

fMRI was performed both under task and at rest, using identical sequences. A blood oxygenation level dependent (BOLD) echo planar imaging (EPI) sequence (T2*-weighted) was used employing TE/TR 35/2000 ms, 195 dynamic whole cerebrum scans, 2 mm × 2 mm in plane resolution, 4 mm thick axial slices (no gap; FOV 256 mm × 256 mm × 128 mm), flip angle 90° and acquisition time 6.5 min. 

fMRI activation paradigms. For each task, a standard block design was used of 6 task condition blocks interleaved with baseline blocks. Each block lasted 30 s and each paradigm started and ended with a baseline block. Tasks were presented visually.

In the word generation paradigm, the children were asked to covertly generate as many words as possible starting with a certain letter (U—N—K—A—E—P, 1 letter per task block). During baseline, an asterisk (*) was presented for visual fixation (Vlooswijk et al., 2010b).

During the reading task, text with a semantic meaning was presented (task block) alternated with nonsense text (baseline condition) (Vlooswijk et al., 2010b). To ensure continuous reading, the text was refreshed 3 times per 30 s block. To minimize the effect of individual differences in reading abilities, each text frame consisted of 4 lines, only the first 2 of which were essential for text continuity.

In the finger tapping task, the children were asked to touch their fingers with their thumb in a consecutive manner. An arrow indicated which hand to use. Right-handed tapping was alternated with left-handed tapping and both were interleaved with the baseline condition (visual fixation). Resting-state fMRI paradigm. For the rs-fMRI scan, the children were asked to clear their mind, lie quietly in the scanner with their eyes closed and to stay awake.

Preprocessing of functional images

All fMRI time series were preprocessed using SPM8 (Wellcome Department of Cognitive Neurology, London, UK). First, the images of each dynamic series were realigned to correct for head motion using rigid transformations. Next, the T1-weighted anatomical image was segmented (gray matter, white matter, and cerebrospinal fluid) and transformed to the standardized stereotactic coordinate system of the Montreal Neurological Institute (MNI). This normalization was applied to the realigned dynamic images to generate movement-corrected normalized fMRI data suitable for group analysis. Finally, the task-related functional images were spatially smoothed using a Gaussian kernel with a full width at half maximum (FWHM) of 6 mm.

Activation analysis

The task-related functional images were analyzed using general linear models (GLMs) in SPM8. The task block design

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was convolved with a standard hemodynamic response function (HRF) to model the BOLD response. For the reading task, reading text with semantic meaning and reading nonsense text were modeled separately. Similarly, left and right handed finger tapping were modeled by 2 independent regressors.

The movement parameters as estimated in the preprocessing were used as confounders to compensate for residual movement.

Significant activation was assessed using t-contrasts of the task regressors. This resulted in activation maps for word generation (task vs baseline), reading (text with semantic meaning vs nonsense text) and left and right handed finger tapping (both vs baseline). A family wise error (FWE) correction for multiple comparisons was applied at $p = 0.05$.

The individual activation maps were combined in a standard random-effects group analysis. For each task, spherical regions of interest (ROIs) were defined at relevant local maxima of the pooled (i.e. patients and controls combined) activation maps. In case of unilateral activation (language tasks), contralateral ROIs were constructed by mirroring with respect to the mid-sagittal plane. This is also motivated by the finding of atypical language lateralization in other types of pediatric epilepsy (Liegelos et al., 2004; Yuan et al., 2006).

### Language lateralization

For both language tasks, the laterality index (LI) distribution was assessed following Abbott et al. (2010). The LI quantifies the extent to which an activation map is left or right lateralized and is defined as

$$LI = \frac{N_L - N_R}{N_L + N_R},$$

where $N_L$ and $N_R$ are defined as the number of voxels above a certain activation threshold ($t$-value) in the left and right hemisphere, respectively. The LI distribution is the LI as a function of the number of activated voxels (for a certain significance level) $N = N_L + N_R$ and is expected to be more sensitive for group differences than assessing LI for a single (fixed) value of $N$ (Abbott et al., 2010). For both language tasks, only activated voxels within their respective activation ROIs (and the contralateral homologue ROIs) were used.

A norm group LI distribution was constructed based on the data from the controls. Abnormalities in patient LI distribution were defined as being outside the 95% confidence interval of the controls group LI distribution (Abbott et al., 2010).

### Functional connectivity analysis

The ROIs of pooled activation for all tasks were used for a resting-state functional connectivity analysis. First, the registered and normalized resting-state data were spatial-temporally filtered using a high pass filter with a cut-off at 0.01 Hz and a Gaussian spatial filter with a FWHM of 5 mm in FSL (FMRIB’s Software Library, Oxford, UK). Next, the data were corrected for the mean brain signal (regressing out the mean brain time series). The average time series of each ROI was calculated, and Pearson’s correlation coefficient was used to quantify the functional connectivity between each pair of time series. These correlation coefficients were Fisher-Z transformed to improve normality and compared between patients and controls using permutation tests (Bassett et al., 2008; van den Heuvel et al., 2010; Zhang et al., 2011). For these network investigations, $p < 0.01$ was deemed significant.

For the connections that proved aberrant in RE, the association with language performance was assessed by calculating the correlation between connection strength and CELF-4 indices.

### Results

#### Neuropsychological assessment (CELF-4)

The core language score of the patients (92 ± 18) was only just significantly below the norm of 100 ($p = 0.047$) and more importantly was significantly lower than that of the healthy controls (106 ± 11, $p = 0.003$). The patients scored below norm on all subtests. These deficits were significant in receptive language (87 ± 19, $p = 0.002$) and language content index (87 ± 18, $p = 0.002$), and a trend of reduced expressive language index was found (92 ± 18, $p = 0.054$).

#### Activation maps

##### Word generation

The word generation paradigm induced activity in the anterior cingulate cortex (ACC) bilaterally and in the left inferior frontal gyrus (IFG) in both groups. No significant group differences were found ($p > 0.05$, FWE corrected), which motivated calculating a pooled activation map, see Fig. 1A.

##### Reading task

The pooled activation map of the reading task is given in Fig. 1B. In both patients and controls, activation is seen in the bilateral temporal lobes. In the left temporal lobe, activation appeared more extended and also had an inferior and perisylvian component. No significant group differences were found.

##### Finger tapping

Finger tapping related activation was seen in the rolndic areas and the cerebellum. No significant group differences were found and the pooled activation map is given in Fig. 1C.

#### Definition of regions of interest in pooled activation maps

Spherical regions of interest (ROIs) were defined at relevant local maxima of the pooled activation maps, as illustrated in Fig. 1. All ROIs had radius 10 mm, except those in the anterior cingulate cortex (5 mm) to prevent interhemispheric overlap.

#### Language lateralization

For the word generation and reading tasks, the LI distributions are given in Fig. 2. Moderately left sided (positive)
Aberrant functional connectivity in RE

Figure 1  Pooled activation maps and spherical regions of interest (transparent white) for (A) word generation; (B) reading; and (C) finger tapping. For word generation, regions of interest are defined in the bilateral anterior cingulate (A1), inferior frontal (A2) and insular (A3) cortices. For reading, regions of interest are defined in posterior (B1 and B2) and anterior (B3) temporal regions. For finger tapping, regions of interest are defined in the bilateral sensorimotor areas (C1–3). In all tasks, activation was also seen in the occipital lobes related to visual task presentation. $p=0.05$, FWE corrected. The underlay is the averaged MNI-registered structural scan of the controls.
lateralization is seen for both, but is more pronounced for the word generation task. In word generation, a trend of more pronounced lateralization is seen for patients compared to controls, however the mean patient curve still lies mostly within the 95% confidence interval of the mean controls curve (Fig. 2A). Also for reading, no aberrant patient lateralization is found (Fig. 2B).

The limited laterality of the language task activations motivated the inclusion of the contralateral homotopic ROIs in the connectivity analysis.

**Functional connectivity**

The group averaged functional connectivity values are visualized as connectivity matrices in Fig. 3. Note that, first, correlation values are mostly positive, suggestive of co-activation of brain regions. Second, connectivity is strongest for within-task ROIs. This is apparent from the relatively high values within the 3 sub matrices along the diagonal (dashed lines), which indicates that (also) at rest the ROIs representing a separate functional network are strongly interconnected. Third, relatively high connectivity is found...
for interhemispheric connections of homologue regions, which is reflected by the relatively high values of the corresponding first off-diagonal elements.

Decreased connectivity in patients compared to controls was found between the left motor ROI and the right IFG (p = 0.006; blue boxes in Fig. 3). This aberrant connection is visualized with respect to anatomy in Fig. 4. For this connection, the connectivity values were correlated with the CELF-4 language indices; significant positive correlations were found for the core language score \( r = 0.49, p = 0.02 \), expressive language index \( r = 0.47, p = 0.03 \), language structure index \( r = 0.43, p = 0.04 \), and working memory index \( r = 0.49, p = 0.02 \), see Fig. 5. Also the data points of the controls are given, as well as the significance level of the individual connections (horizontal lines). Ten controls showed significant positive connectivity vs 1 showing significant negative connectivity; for the patients this was 4 vs 6, respectively.

**Discussion**

**Major findings**

In this study, we employed fMRI to find a functional correlate for language impairment in RE. Based on CELF-4 performance, we identified language impairment in a clinical population of children with RE. Activation map analysis of expressive and receptive language tasks revealed no significant differences but an essentially bilateral distribution of activation at the age range under study (8–14 years).

Reduced functional connectivity was found in patients compared to controls for a connection between the motor and the language network. In addition, the strength of this aberrant connection decreased significantly with poorer language performance in children with RE. Both findings indicate that this aberrant connection links rolandic (sensorimotor) pathology to language impairment in RE.

**Language impairment profile**

The language impairments identified in the children with RE involved both a reduction in core language score and specific impairments in receptive language and language content index. Especially since these impairments were not only found with respect to matched controls but also compared to (global) norm values, these findings imply that in a clinical population of children with RE (i.e. characteristic EEG and seizure semiology), language impairment is detectable at the group level. In earlier work, a strict distinction was made between benign and complicated cases, only the latter showing cognitive impairments (Massa et al., 2001). However, in line with our findings, language impairment has recently been described as a general feature of RE (Lillywhite et al., 2009) and, even more broadly, of nocturnal epileptiform activity in children in general (Overvliet et al., 2010, 2011b). Children with RE have been described to underperform especially in sentence production and comprehension (Lillywhite et al., 2009; Overvliet et al., 2011a), which is in analogy with the impaired language content index we report.

**Bilateral global language activation**

No activation map differences were found. This indicates that in RE, globally the same regions are involved in word
generation, reading and finger tapping as in healthy controls. This is in line with the fMRI study of Lillywhite et al. (2009), which reports typical patterns of language-related activation in both children with RE and controls using a verb-generation task. The absence of abnormalities with respect to activation maps motivated the use of more advanced analyses in finding functional abnormalities in RE. Abnormalities in functional connectivity in combination with normal language activation patterns have been found in epilepsy patients before (Vlooswijk et al., 2010b).

No differences in language laterality were found and lateralization showed only a slight left predominance in both patients and controls. This is not surprising for this age range (8–14 years) as adult-typical left hemisphere lateralization emerges gradually from an initially bilateral language network (Kadis et al., 2011). This motivated the inclusion of the contralateral homotopic ROIs of the language tasks in the connectivity analysis.

Abnormal functional connectivity

Functional connectivity analysis revealed a hypo connectivity in children with RE compared to healthy controls. Previous EEG research has demonstrated that in epileptogenic networks, local increases in synchronization during seizures are associated with decreased functional connectivity in the interictal state (Ponten et al., 2007, 2009; Vlooswijk et al., 2010a). Therefore, the left motor–right IFG hypo connection might facilitate the ictal spread of seizure activity. A stronger interictal connectivity reduction might be associated with more severe pathology and consequently more pronounced language impairment. In line with this, lower connectivity was associated with reductions of several language scores for this connection. Furthermore, the fact that significant connectivity values were usually positive in controls and negative in patients (Fig. 5) suggests that the nature of left motor–right IFG connection changes from facilitatory to inhibitory in RE.

Note that given the current findings it is not possible to say whether rolandic epilepsy causes abnormalities in functional connectivity, or whether both are epiphenomena of an underlying epileptogenic process. The interactions between seizures, interictal epileptiform activity, and brain structure and function are highly complex, and their causal relations form an extensive field of research on their own (Jacobs et al., 2009).

Some light may be shed on this matter by work on EEG data. From EEG literature it has long been known that epileptiform spikes may reduce the amplitude and increase the latency of directly subsequent evoked potentials (Seri et al., 1998; Shewmon and Erwin, 1988). Especially the inhibitory phase (corresponding to the EEG slow wave) following the spike extensively interferes with neuronal processing, not only locally, but also in distant regions such as contralateral homotopic cortex and the thalamus (Shewmon and Erwin, 1988). It is these distal and relatively long lasting (slow wave mediated) effects that may actually be picked up by resting state fMRI analyses of connectivity between distributed regions, such as the work presented here. More specifically for the role of (nocturnal) epileptiform EEG discharges in language impairment in children, we refer to the review by Overvliet et al. (2010).

It has already been mentioned that in RE the language impairments may persist even after (spontaneous) seizure remission (Kanemura and Aihara, 2009; Monjaue et al., 2011). A mechanism that has been suggested for this in the related Landau–Kleffner syndrome (LKS) is that the epileptiform activity initially may interfere directly with language functionality, and secondarily induces focal atrophy which causes irreversible language impairment which persists after seizure remission (Bourgeois & Landau, 2004; Takeoka et al., 2004). More generally, RE (and LKS) may strike the brain at a critical age window of development, and may offset the normal trajectory of functional network formation (Andersen, 2003). To gain more insight in this, for future research longitudinal study designs are recommended to investigate how EEG abnormalities, aberrant functional connectivity, and language impairment manifest themselves over time in RE.

For clarity, we repeat that the laterality analysis demonstrated the language network to be essentially bilateral in the age range under study (8–14 years), which is in line with literature on brain development (Kadis et al., 2011). As a consequence, aberrant connectivity between a motor area and the right hemisphere homologue of Broca’s area should still be considered a connectivity abnormality between the motor and the language system. This insight is essential in understanding the aforementioned abnormalities in functional connectivity and their significance with respect to language function.

Methodological issues

Although in the current study expressive and receptive tasks were used to identify the major language networks, this approach does not guarantee inclusion of all possibly relevant language mediating areas. For future research it would be interesting to use specifically tailored tasks to find networks with functional connections related to specific aspects of language impairment in RE.

Alternatively, to avoid the bias caused by the investigation of sparse task networks, resting-state data could be used to define networks based on spatial patterns of similar time series using independent component analysis (Besseling et al., 2013; Calhoun et al., 2009) or using a large number of anatomical regions of interest (e.g. gyral pattern based, Dale et al., 1999; Fischl and Dale, 2000).

In addition, for the pathophysiological interpretation of the aberrant functional connections identified in this study, we suggest to investigate the integrity of the structural white matter connections involved (Basser et al., 1994; Jones, 2010).

Finally, in our connectivity analysis, we employed a relatively strict p-value threshold of p=0.01. Future studies employing a more formal correction for the number of connections involved are warranted to validate the robustness of our findings.

Conclusion

We demonstrated language impairment in children with a clinical diagnosis of RE (seizure semiology and EEG based),
which is indicative of language impairment in the general RE population. Connectivity analysis demonstrated abnormalities whereas activation did not, possibly indicating that probing the integrity of and interplay between functional networks is more sensitive than studying their (individual) spatial patterns. These findings provide a functional correlate for the neuropsychological profile of notably language impairment as described in the RE literature before. More specific, reduced functional connectivity was identified between a language and a sensorimotor region, indicating a disturbed interplay between language and motor networks in RE. In line with this, lower connectivity values were associated with lower language scores in the patient group. The exact causal relationship between seizures and/or interictal epileptiform activity and abnormalities in functional connectivity in RE is beyond the scope of this study, and remains an important subject for future research with respect to unveiling the exact pathological mechanism, preferably employing a longitudinal design.

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