PhD project proposal
neural correlates of handwriting (training)

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General backgrounds and timeline of the project

In this report, I will describe the proposal for my PhD study. The project will involve three phases.

In the first phase (years 1 and 2), a study of the neural correlates of handwriting in grade 3 and 4 children with and without handwriting problems (HWP) will be performed. The neural correlates will be tested with structural magnetic resonance imaging (sMRI), functional magnetic resonance imaging (fMRI), resting state fMRI (rs-fMRI), and diffusion tensor imaging (DTI) scans. In the parallel second phase (year 1 and 2), software will be developed or selected, in which writing patterns and handwriting are trained.

The software is meant as an addition to conventional physiotherapist handwriting intervention, and in phase 3 (year 3 and 4) it will be applied as an intervention for grade 2-4 HWP children in eight weekly 1 hour sessions for eight weeks. Before and after intervention, children will be scanned using sMRI, fMRI, rs-fMRI, and DTI.

All in all the study will provide major insights in the organisation of handwriting in the brain of children. Through enhanced insight in the components of handwriting, this may provide targets for improvement of existing HWP interventions.

Phase 1 neural correlates of children’s handwriting

Backgrounds

From the first year of kindergarten, (pre-)writing skills are taught. Education of handwriting often intensifies from grade 1 and continues until the end of primary school. [1] This is not very surprising, because handwriting is very important. Poor handwriting skills can result in illegible, slower, or incomplete written communication of knowledge and through this impaired handwriting can negatively affect academic achievement [e.g., 2,3,4,5].

Prevalence of handwriting problems (HWP)

Problems with handwriting occur in 5-33 % of school-going children [6,7,8]. HWP prevalence has been studied in 70 grade 2 and 169 grade 3 children [7]. It was found that HWP prevalence decreased from 37% in November of grade 2, to 17% in May of grade 2, and finally to 6% in November and May of grade 3. [7] This indication that prevalence may be higher in grade 2 and then drops in grade 3 is supported by the high prevalence of 28% found in 218 Dutch grade 2 children [9]. Moreover, stabilisation to a prevalence of 5-6% is plausible, as prevalence values of 5.25 and 6% were found in 1312 and 125 children, respectively [8,10]. The high HWP prevalence of 5 to 33% should be reason enough to further investigate HWP.

Handwriting quality assessment and diagnosis of HWP

Various handwriting assessment tools have been developed to assess handwriting quality, and to ultimately diagnose HWP [6]. Two important validated Dutch assessment tools are the *Concise Assessment Method for Children's Handwriting* (BHK)[1] and the *Systematic Screening for Handwriting Difficulties* (SOS)[2]. BHK can be used to define handwriting quality in grades 2 and 3, while SOS is applicable in children of 7 to 11 years old. [6,7,11,12].

The BHK test has been repeatedly used to assess the quality or speed of handwriting and to identify children with handwriting problems[3] [e.g., 8,13,14,15,16]. The test involves copying part of a standard text of 302 words and 1444 letters within 5 minutes. The first five lines (20 words and 56 letters) of the copied text are assessed on 13 aspects of the handwriting quality. These aspects are related to spatial characteristics, e.g., how letters and words are spaced, and letter form, e.g., letter shape and size. Each of the 13 aspects can be scored 0 to 5, and larger scores reflect lower handwriting quality [9,15,16].

Scores of ≥ 29, 22-28, and ≤ 21 respectively reflect dysgraphic, at risk of dysgraphic and good handwriting. [7,9,14,16] Sadly, the BHK is no longer in press and therefore it has limited availability [6]. Moreover, assessing the quality of the copied text requires extensive training and takes 15 to 20 minutes for an experienced tester and [6,12].

In the shorter, more efficient SOS test, children copy part of a standard text of 399 words and 1634 letters within 5 minutes [6,11,12]. The quality of the first five lines (21 words and 56 letters) is assessed according to the following six criteria:

1) letter formation fluency
2) letter connection fluency
3) letter height
4) letter height regularity
5) inter-word spaces
6) sentence straightness or –regularity.

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[1] In Dutch: 'Beknopte beoordelingsmethode voor kinderhandschriften'

[2] In Dutch: 'Systematische Opsporing Schrijfproblemen';

[3] Handwriting problems are also referred to as dysgraphic, non-proficient, or very poor handwriting [6,8,9,15].

The items can be scored 0 to 2 and the maximum score is 12, with higher scores reflecting poorer handwriting. SOS scores were standardized by investigation of SOS-defined handwriting quality in 880 children (438 boys and 422 girls; see table 1).

Table 1 SOS scores of Van Waelvelde et al [11]. This table depicts the SOS quality scores of the 3, 5 and 15% lowest scoring children, respectively referred to as ≤3%, ≤5% and ≤15%. In the fifth column the scores of the 85% highest scoring children, referred to as ≥85%, are presented.

	≤ 3%	≤ 5%	≤ 15%	≥ 85%
7 year olds (215)	≥ 8	≥ 7	≥ 6	≤ 5
8 year olds (290)	≥ 7	≥ 6	≥ 5	≤ 4
9 year olds (120)	≥ 7	≥ 6	≥ 4	≤ 3
10 year olds (114)	≥ 6	≥ 5	≥ 4	≤ 3
11-12 year olds (121)	≥ 5	≥ 4	≥ 3	≤ 2

Handwriting speed assessment

BHK and SOS are not only applicable to assess handwriting quality, but also to assess overall handwriting speed. This is done by counting the letters that are written within five minutes.

Using of the digitizing tablet to assess kinematic and spatial properties of handwriting

Investigation of more subtle kinematic and spatial differences at the letter or stroke level may provide extra insight in the difference of the handwriting movement and product between children with and without HWP. These subtle differences can be investigated with the digitizing tablet[4] [14,17,18]. The digitizing tablet is an electronic surface that can be written on with an electronic pen. The tablet simultaneously records where (x and y coordinates) and when the pen touches the surface[5] [17]. Using this tablet the exact duration, mean velocity and trajectory length per letter or stroke can be defined [e.g. 14,18].

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[4] the digitizing tablet is also referred to as the graphics tablet or the digitizer.

[5] because it records the x- and y- coordinates of pen/surface contact, it is also known as the x-y digitizer.

Differences in handwriting between children with and without HWP

Children with HWP differ from children without these problems in the variability of the speed and overall quality of their handwriting [e.g., 6,13,14,18,19]. For instance, Graham et al. [19] found that children with HWP differ from children without HWP in the accuracy and variability of letter form, letter size and letter spatialization characteristics. [19]. Additionally, Dynamic Time Warping (DTW) calculations were used to reveal increased letter form variability. [14]

Van Galen et al. [18] collected kinematic handwriting data, using a digitizing tablet. Then, they used Power Spectral Density Analysis (PSDA) to calculate power in the velocity peak frequency range of 1-49 Hz in steps of 3 Hz, and power differences between children with and without HWP were assessed. They found significant increases in absolute power values at frequencies of 1 to 46 Hz in children with HWP, indicating more noisy handwriting movements. As these frequencies are easily contaminated with velocity peaks that are related to movements that are required to adequately write the word, relative power spectra were also calculated. They found **decreased** relative power from 1-4 Hz and **increased** relative power from 4-10 Hz in children with HWP. [18] The decreased power was in frequency bands that represent controlled movement (0-5 Hz), while the increased power was mainly in bands that represent movement tremor (5-10 Hz). This suggested increased neuromotor noise in HWP children. [13,18] The number of noisy peaks in the handwriting movement can be calculated by subtraction of the number of peaks involved in controlled writing movements (which remain after filtering with the cut-off frequency of 5 Hz) from those involved in controlled and noisy writing movements (which remain after filtering with the cut-off frequency of 10 Hz). The resulting value is called the Signal-to-Noise velocity peaks difference (SNvpd). Increased SNvpd was found in children with HWP, suggesting increased neuromotor noise [13].

Although there are indications that overall handwriting speed is slower in children with HWP [7,16,17,20], there is also contradictory evidence [8,9,14]. Using the digitizing tablet, letter or stroke time, velocity and trajectory length were evaluated in short and simple handwriting tasks [14,17,18]. Some studies found similar stroke writing durations, but increased stroke velocities and trajectory lengths in children with HWP [14,18], but another study revealed increased duration of letter writing and decreased velocity for both short and long handwriting tasks in children with HWP [17]. Interestingly, Rosenblum et al. [17] found that children with HWP had a significantly more time-consuming "in air" trajectory[6] than children without HWP. This may mean that part of the potential speed differences is explained by increased in air time.

Visual-motor integration and fine motor skills as underlying components of HWP

Regarding the differences between children with and without HWP, it is now important to discuss two important components of handwriting, i.e., visual-motor integration (VMI), which is the coordination of motor output with visual input, and fine motor coordination [e.g., 15,21,22,23,24]. Research indicates that children with HWP have reduced VMI- and fine motor skills [e.g., 16,22,23,24]. Interestingly, handwriting quality is associated with VMI in children with HWP, while it is associated with fine motor coordination in children without HWP [16].

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[6] "in air" trajectory: when the pen is above –and not on- the writing surface.

Neural correlates of handwriting in adults

The neural correlates of handwriting are important, as they may provide a more comprehensive insight in the underlying problems of handwriting, and more insight may result in new, more successful intervention targets. Therefore, we will now discuss the neural correlates of handwriting. The neural correlates of handwriting can be understood, using three underlying processes of handwriting include *input processes*, *writing or spelling specific processes*, and *motor output* (for the full description, see fig. 1). [25]

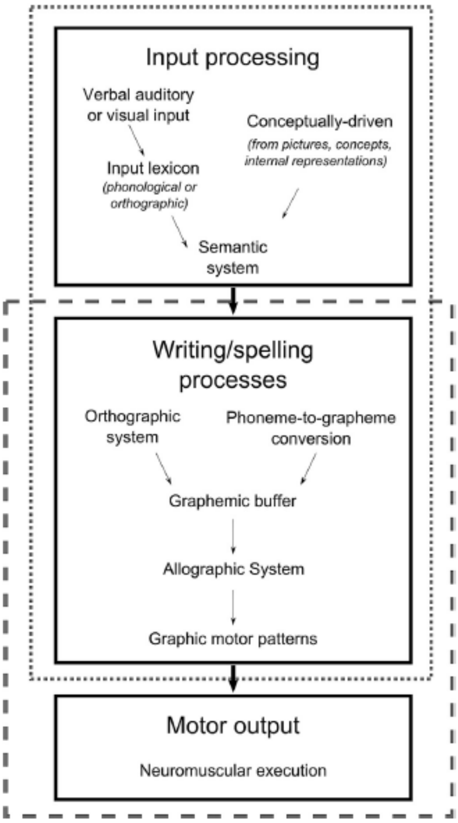

Figure 1. cognition: During *input processing* the writing unspecific linguistic processes take place, in which verbal input or conceptually driven information is coupled to meaning. Concepts are directly coupled to meaning, while verbal or visual input is coupled to meaning via the input lexicon. In *writing-specific processes*, semantics are converted in word level orthographic information (lexical route) or sounds are directly coupled to letters via phoneme-to-grapheme conversion (sublexical route). This information is temporarily stored in the graphemic buffer. Allographic processes convert the information into word/letter forms and in graphic motor pattern plans. These plans are executed during *motor output*. **fMRI:** in contrasts of writing with motor output (e.g., circle drawing) the processes within the dotted lines remain; in contrasts of writing with general input- or linguistic processes (e.g., reading aloud) the dashed line encased processes remain. Neural correlates active in both contrasts are likely involved in dashed-dotted processes, i.e., in writing-specific processes.
Taken from Planton et al. [25]

Planton et al. [25] performed a meta-analysis on 18 neuroimaging studies. These neuroimaging studies examined contrasts of writing with motor output, of writing with linguistic input, or of writing with rest. In this meta-analysis activation likelihood estimates (ALE) were calculated for all contrasts, for all writing>linguistic input contrasts and for all writing>motor output contrasts. [25]

Motor output is controlled for in fMRI contrasts of writing with motor tasks (e.g., circle drawing), while input processing is controlled for in fMRI contrasts of writing with input processes (e.g., spoken reading; see fig. 1). Neural correlates that are active only for handwriting>linguistic input and handwriting>motor output contrasts, respectively represent the neural correlates of motor output processes and of linguistic input processes. Those neural correlates that are active for both contrasts are involved in writing-specific processes (fig. 1) [25].

Thus, the brain areas involved in handwriting-specific processes were (fig. 2 & table 2) [25]:

- left superior frontal area, including middle frontal gyrus, superior frontal sulcus (**MFG**/**SFS**);
- left superior parietal area, including left inferior parietal lobe (**IPL**), intraparietal sulcus (**IPS**), and superior parietal lobule (**SPL**);
- right posterior lobe of cerebellum

Additionally, the neural correlates of motor output processes were (fig. 2 & table 2) [25]:

- left precentral gyrus, primary motor and sensorimotor cortex (**preCG**/**M1**/**SM1**);
- left medial frontal gyrus, (pre-)supplementary motor area (**medFG/[pre-]SMA**);
- left thalamus;
- left putamen;
- right anterior lobe of cerebellum

Finally, the following brain areas were involved in linguistic input processes (fig. 2 & table 2) [25]:

- left ventral premotor area, inferior frontal gyrus (**vPM**/**IFG**);
- left fusiform gyrus, posterior inferior temporal cortex (**PITC**).

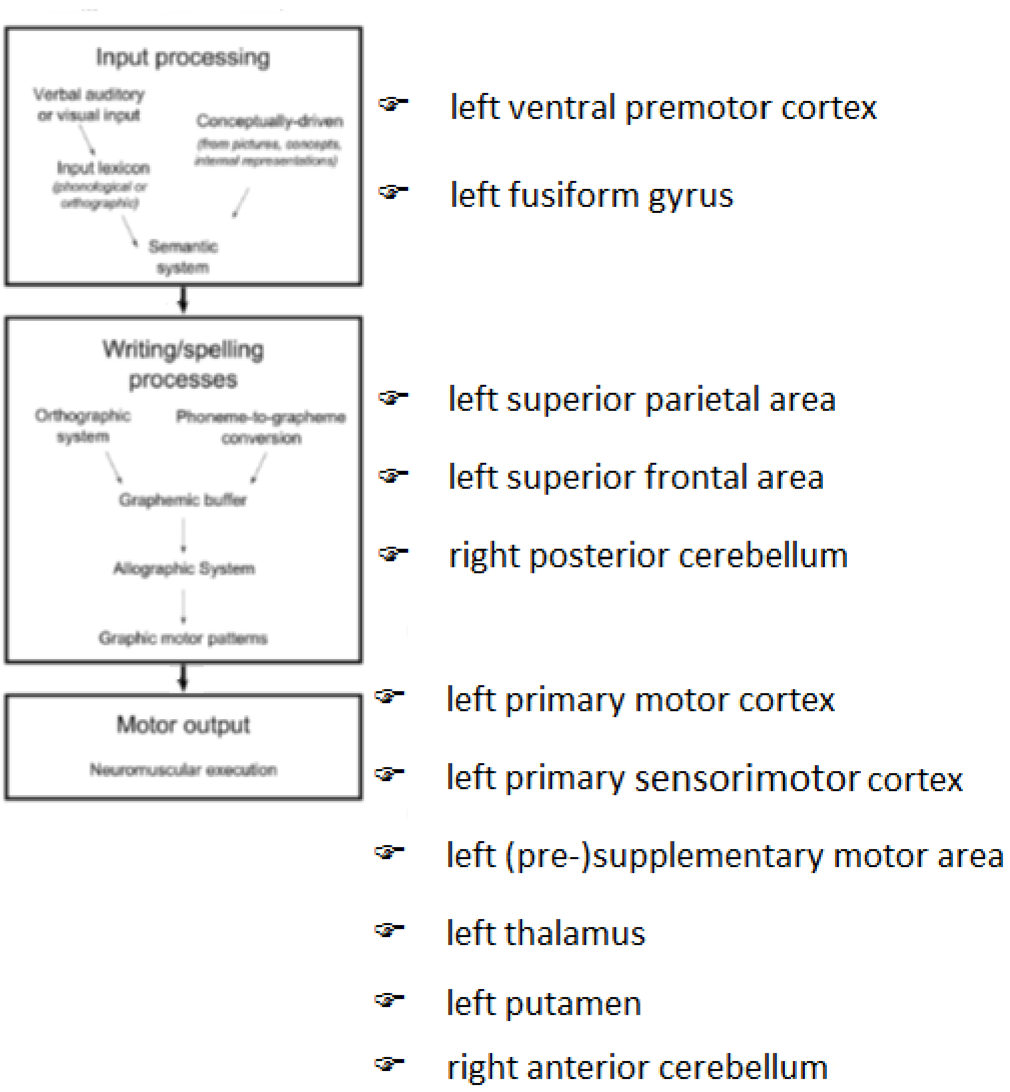

Figure 2. Neural correlates of writing in adults. [25] Input or linguistic processing seems specifically related to activity in the left ventral premotor area and left fusiform gyrus. Left superior parietal area, left superior frontal area and right posterior cerebellum seem to be involved in writing-specific processes. Left primary motor and sensorimotor areas, left (pre-)SMA, left thalamus, left putamen and right anterior cerebellum are involved in motor output specific processes.

The motor output- and writing-specific brain areas are probably involved in the actual handwriting movement. Thus, left-lateralized superior frontal area, M1, SM1, SMA, superior parietal, thalamus and putamen and right-lateralized anterior and posterior cerebellum are probably involved in the handwriting movement. Activity in the linguistic input-specific areas, including left vPM/IFG and PITC may also play a role in handwriting, but it probably represents higher order processes and not the actual writing movement. Activity in these areas could be associated with increased “in air” time in children with HWP.

Table 2 areas involved in (hand)writing. 👍 refers to good writers, while 👎 refers to poor writers. 👍/👎 means a brain area was active in good or poor writers, as no distinction was made in the study. 👍>👎 means there was larger activation in good writers than in poor writers. 👍&👎 means there is activity in good and poor writers, while 👍 and 👎 respectively refer to activity only present in poor or good writers. ☒ refers to absent activity. *’s refer to activity that was found to associate with handwriting scores. For Richards et al. [26] we only specifically report areas that correlate with handwriting skills or that overlap with results from Planton et al. [25] or Richards et al. [27].

Brain area	Planton et al. (2013)	Richards et al. (2009)	Richards et al. (2011)
left superior frontal area, including MFG/SFS	👍/👎	👍>👎	☒
left ventral premotor cortex	👍/👎	☒	☒
left (pre-)SMA	👍/👎	👍>👎	☒
left primary motor cortex	👍/👎	☒	👍
left primary somatosensory cortex	☒	👍>👎*	👍
left superior parietal area, including IPL/IPS/SPL	👍/👎	👍>👎*	👍 (IPL), 👎 (SPL)
left precuneus	☒	👍>👎*	👎
left cuneus	☒	👍>👎	👎
left calcarine gyrus	☒	👍>👎	👍&👎
left lingual gyrus	☒	👍>👎	👎
left superior occipital area	☒	☒	👎
left middle occipital area	☒	👍>👎	👎
left supramarginal gyrus	☒	👍>👎*	☒
left superior temporal area	☒	👍>👎*	☒
left middle temporal area	☒	👍>👎*	☒
left fusiform gyrus (or left posterior inferior temporal cortex)	👍/👎	👍>👎	👎
left inferior temporal area	☒	👍>👎*	☒
left posterior cingulate gyrus	☒	☒	👎
left middle cingulate gyrus	☒	👍>👎*	☒
left anterior cingulate gyrus	☒	👍>👎*	☒
left thalamus	👍/👎	👍>👎	☒
left putamen	👍/👎	☒	☒
right posterior cerebellum	👍/👎	👍>👎	👍&👎
right anterior cerebellum	👍/👎	👍>👎	👍&👎
right superior frontal cortex	☒	👍>👎*	☒
right middle frontal cortex	☒	👍>👎*	☒

right inferior frontal cortex (orbital part; would be part of broca’s area in left hemisphere	☒	👍>👎*	☒
right precuneus	☒	👍>👎*	👎
right cuneus	☒	👍>👎	👎
right calcarine gyrus	☒	👍>👎	👎
right lingual gyrus	☒	👍>👎	👍&👎
right supramarginal gyrus	☒	👍>👎*	☒
right superior temporal gyrus	☒	👍>👎*	☒
right middle temporal gyrus	☒	👍>👎*	☒
right inferior temporal gyrus	☒	👍>👎*	☒
left posterior cerebellum	☒	👍>👎*	👍&👎
left anterior cerebellum	☒	👍>👎	👎

Neural correlates of handwriting in children

Although the neural correlates of handwriting in adults are well-known, there is only limited insight in the neural correlates of handwriting in children. The available fMRI studies in children have investigated the brain activity in HWP and in absence of it [26,27]. These studies have researched the neural correlates of successive finger tapping (suTap) contrasted with single finger tapping (siTap) [26], and of simple pseudoletter writing (pseuL, i.e., drawing a circle with a line above it) contrasted with writing an actual letter (LET; namely, ‘ɑ’) [27]. Because suTap is strongly associated with handwriting, both suTap>siTap and pseuL>LET contrast-related brain activities are implicated in the motor aspects of handwriting (see table 2). However, suTap>siTap only represents neural correlates of handwriting indirectly. Therefore, only those suTap>siTap related brain activations that are associated with handwriting skills or that have also been found in other handwriting studies are reported in table 2 [25,26,27].

In general, the neural correlates of handwriting in children were more widespread than those in adults. Additionally, there was widespread activity in the right cerebral and left cerebellar hemisphere, suggesting that brain lateralization may not have fully developed yet in children. Importantly, like adults, children seem to activate left superior frontal area, left (pre-)SMA, left M1, left superior parietal area, left fusiform area, left thalamus and right posterior and anterior cerebellum. The role of individual areas that were active for pseuL>LET and suTap>siTap (see table 2) in actual handwriting remains uncertain, as pseuL>LET and suTap>siTap respectively represent brain activity related to newly learned letters and brain activity related to indirect handwriting representations. After all, in actual handwriting, children write practiced letters.

Although the neural correlates of handwriting in adults are not necessarily involved in handwriting of children, they represent practiced handwriting of texts better. Thus, the neural correlates of handwriting in adults will be selected as regions of interest (ROIs) in the current study. However, because of the possible immature brain lateralization in children, we will investigate these ROIs bilaterally. Moreover, as literature in children suggests more widespread brain area involvement in children than in adults, we will additionally perform whole brain analysis in the task-related fMRI (t-fMRI) part of the experiment. The involved brain areas that are found in t-fMRI will then be investigated in the rs-fMRI and DTI parts of the experiment.

Research question

The research question for this part of the project is: **“what are the neural correlates of handwriting in children, and how do they differ between children with and without HWP?”**

Methods

Participants

For the pilot, we will recruit 3 healthy children, and for the actual experiment we will recruit 14 children with- and 14 children without HWP from grades 3 and 4 of seven elementary schools. Teachers of each grade will be asked to recruit one child with HWP diagnosis and one child without it. If necessary, children in grades 3 and 4 of these schools will be screened for HWP using SOS, and subsequently diagnosed with HWP (or not) by physiotherapists.

General procedure

In the current experiment we will first measure handwriting skills. After that, the neural correlates of handwriting will be evaluated using sMRI, fMRI, DTI and rs-fMRI.

During data analysis, we will analyse the neural correlates of handwriting, compare them between children with and without HWP, and investigate their associations with measures of handwriting skills.

This procedure will be executed for the pilot ant the actual experiment. During the pilot, the experimental parameters will be fine-tuned.

Behavioural assessment

In this experiment, text copying will be assessed, because we expect that copying a text involves less cognitive processing than writing to dictation and generative writing. After all, we are mainly interested in the motor component of handwriting.

Children will copy the text of the SOS for five minutes. Additionally, children will copy the first two sentences of the BHK test (i.e., “jan is bij oom, hij eet ijs”) ten times. Both tasks will be performed with an electric pen on a digitizing tablet.

We will additionally assess VMI, visual perception (VP) and motor coordination (MC) skills, using the Developmental Test of VMI (Beery VMI). Beery VMI has good validity, and assessment takes 10-15 minutes. [6]

Regarding the duration of behavioural assessment, repeating the sentence “jan is (…)” 10 times entails writing 170 letters. To predict how long this takes estimates of handwriting speed in children with and without HWP were required. For this purpose, handwriting speed was defined by calculation of weighted means of handwriting speeds found in seven studies [7,8,9,16,17,20,28]. Handwriting speeds were estimated to be 20.6 letters/minute in children with HWP and 28.7 letters/minute in children without HWP. Based on these speed estimates, writing 170 letters will take on average 8.2 minutes in HWP children and 5.9 minutes in no HWP children. Ten minutes would therefore be a safe estimate of the duration of copying “jan is (…)” ten times. We expect that behavioural assessment will maximally take 30 minutes.

Neural assessment

The neural assessment will include sMRI, task-related fMRI (t-fMRI), rs-fMRI and DTI scans.

s-MRI

Structural MRI (sMRI) is required to localize brain activity and connectivity. For these scans parameters of Reitz et al. [29] will be used. These parameters are: repetition time (TR)=7.6 ms, echo time (TE)=3.5 ms, voxel size= 1 x 1 x 1 mm, 176 slices, and field of view (FOV)= 256 x 256 x 176 mm. Scanning will take 5.5 minutes.

t-fMRI

The parameters that were applied by Reitz et al. [29] can be taken as a starting point, because these parameters were successfully used to measure writing-related brain activity. Those were: TR=2000 ms, TE=25 ms, voxel size= 3 x 3 x 3 mm, 33 slices, and a FOV of 240 x 240 x 99 mm. The total fMRI scanning duration will be 30 minutes.

During scanning, participants will perform writing tasks on a fMRI-compatible tablet, which allows precise assessment of the writing movement [e.g., 29]. If it is possible to measure kinematic and spatial aspects reliably using the tablet, measures of these aspects will be used to assess associations of handwriting with brain activity.

During scanning, various tasks will be performed in a blocked design, which includes four block types:

A. written copying – 60 seconds
B. spoken reading – 60 seconds
C. circle drawing – 60 seconds
D. rest (fixation) – 60 seconds

These blocks will be part of five runs, which have two possible sequences: AD-BD-CD (3 runs) and CD-BD-AD (2 runs). Each run will take 6 x 60 = 360 seconds, corresponding with six minutes. This means that the total duration of five runs will be 30 minutes.

We based this design on two neuroimaging studies, which found significant writing-related brain activity when adults wrote 48-147 letters in 15-60 seconds [30,31]. Thus, production of 48-147 letters seems sufficient to successfully assess the neural correlates of handwriting. In the current experiment, children will write for a total duration of five minutes. Based on the writing speed estimates of 20.6 and 28.7 letters/min, HWP and no HWP children will respectively produce on average 103 letters and 143.5 letters. These numbers are within the 48-147 range and are seemingly sufficient.

rs-fMRI

Using similar scanning parameters as in de t-fMRI we will perform a resting state fMRI scan. Scanning will take approximately 10 minutes.

DTI

Caeyenberghs et al. [32] successfully associated white matter integrity (measured through fractional anisotropy; FA) with visual-motor tracking performance in young traumatic brain injury patients. Therefore, we will use their DTI parameters as a starting point. These parameters are: TR=7916 ms, TE=68 ms, FOV=220 x 220 mm, parallel imaging factor=2.5, 68 sagittal slices, voxel size= 2 x 2 x 2.2 mm. Additionally, we will apply two diffusion gradients along 45 non-collinear directions, with diffusion weighting of 800 s/mm^2, and one additional image without diffusion weighting. DTI scans will take about 15 minutes.

Duration of the behavioural and neural assessments

The behavioural measurements will take 30 minutes, and the subsequent sMRI, t-fMRI, rs-fMRI and DTI scans will respectively take 5.5, 30, 10, and 15 minutes. Thus, children will be in the lab for ± 1 hour and 30 minutes, including a scanning duration of 60.5 minutes.

Behavioural data analysis

The produced texts will be assessed for legibility using the SOS legibility criteria. We will also assess overall speed by counting the letters produced in five minutes. Average durations (including “in air” and “on paper” time), velocities and stroke length per letter will also be calculated. Finally, VMI, VP, and MC component scores of the Beery VMI will be acquired.

Using PSDA, we will define the average power spectra of the 10 repetitions of “jan is bij oom, hij eet ijs”. In this analysis, we will define four power values in the frequency range of 1 to 10 Hz, i.e., average absolute and relative power in the 1-5 Hz and 5-10 Hz ranges. We will additionally assess sentence form variability (DTW) and average SNvpd of these sentence repetitions. These same measures will be used to assess exercise effects by comparing the last five repetitions with the first five.

t-fMRI data analysis

The t-fMRI data will first be preprocessed . After that, the contrasts of writing with spoken reading (**A>B**), and of writing with circle drawing (**A>C**) will be analysed.

As described in the backgrounds, areas active only for the **A>B** contrast, areas active only for the **A>C** contrast, and areas active for **both contrasts** respectively represent motor output-specific, linguistic input-specific, and writing specific neural correlates.

The brain areas involved in adult handwriting (fig. 2), namely the right-lateralized anterior and posterior cerebellum, and the left-lateralized superior frontal area, vPM/IFG, medFG, preCG, superior parietal area, PITC, thalamus, and putamen, will be included in ROI analysis of brain activity corresponding to the A>B and A>C contrasts. Additionally, based on apparent immature lateralization in children, all ROIs will be examined bilaterally. Because brain activity in children was widespread, we will additionally perform whole brain analysis.

rs-fMRI data analysis

Firstly, preprocessing of the rs-fMRI data will take place. After that, rs-fMRI data will be analysed using the Graph-Theoretical Analysis Toolbox (GAT) of Hosseini et al. [33]. From the 90 areas of interest of the anatomic automatic labelling (AAL) template [33], those areas that are found to be involved in handwriting in the t-fMRI study will be selected as nodes. Then, the links between the nodes, and the hubs (crucial components) in the resulting network will be defined. Using GAT, this functional connectivity network will be assessed for network segregation (clustering coefficient; C), network integration (characteristic path length; L), and resistance against random failure or target attack of nodes.

In analysis of DTI data we will examine white matter integrity in the white matter tracts connecting the areas that are involved in the handwriting network based on our t-fMRI and rs-fMRI data. White matter tract integrity will be measured through FA and mean diffusivity (MD).

Additionally, the data analysis methodology described by Shu et al [34,35] will be used to apply graph analysis on the DTI data. Using this approach, the underlying structural connectivity of the functional connectivity network shall be examined. Measures of network segregation (C), network integrity (L), resistance against random failure and resistance against target attack will subsequently be examined.

How the neural correlates of handwriting will be defined using t-fMRI

In the t-fMRI experiment the active brain areas for the contrasts are probable neural correlates of (aspects of) handwriting. Associations of activity in these brain areas with the described behavioural measures will solidify their roles in handwriting. Finally, differences in brain area involvement between children with and without HWP will be examined.

How the neural correlates of handwriting will be defined using rs-fMRI and DTI

Through examination of the association of the variables of functional and structural connectivity (i.e., C, L, attack and failure resistance) with the described behavioural measures, we will assess involvement of the network in handwriting. The role of the network can be further solidified by comparing it between children with and without HWP.

Additionally, associations between handwriting skills and individual structural and functional connections between areas involved in handwriting will be examined, to investigate their individual roles in handwriting. Again, differences between children with and without HWP in these individual connections will be examined and interpreted.

Relevance of phase 1

In the experiment of phase 1, we will answer the research question “what are the neural correlates of handwriting in children and how do they differ between children with and without HWP?”

As very little is known about the neural correlates of handwriting in children, this will provide a major contribution to the field of handwriting. Additionally, handwriting is an activity that couples cognitive processes with motor processes through writing-specific processes. We expect that writing-specific neural components of handwriting (found in adult neural correlates of handwriting research and possibly in the currently proposed t-fMRI experiment) are hubs in the neural network of handwriting. If these areas are hubs, this solidifies their potential role in coupling linguistic and cognitive input with motor output. Through these potential findings of how cognition is coupled to motor output, we will provide a major contribution to the field of neuroscience.

Either way, the current study may provide the important first step to a full understanding of the brain areas involved in the different components of handwriting in children. An important second step may be the study of how brain areas change as children are trained in handwriting. We will study this in the third phase of the project, and the data from this phase will be used to define those behavioural measures that are associated most strongly with brain activity or connectivity. This makes this neural correlate study a crucial part of my PhD project.

Phase 2 development of handwriting exercise software

Backgrounds

Development of new software to exercise handwriting is important, because of the high prevalence (5-33%) of handwriting problems (HWP), and because the software is needed for the third phase of the project. Exercises in this software should target (underlying problems of) handwriting. Exercises should also entail successful aspects of handwriting interventions.

Firstly, it is important to note that conventional physiotherapy is aimed at the individual problems of the patient, and depending on these problems intervention components are selected [6,8]. As conventional handwriting intervention is individually aimed, it will not be ethical to develop a treatment that is similar for all participants. On the other hand it is unlikely that interventions that are different for each participant will result in significant brain changes on the individual level. Therefore, we will develop software that is a potential supplement to individual training, and can be used to exercise handwriting at home. However, to our knowledge no studies are available that investigated supplemental therapies. We therefore assume that supplemental exercise or training requires similar principles as the actual intervention.

Underlying aspects of handwriting

As described, association of handwriting with VMI in children with HWP and with fine motor abilities in children without HWP have been found. Therefore, it would not be unreasonable for training to target VMI. Interestingly, freely available handwriting pattern worksheets seem to target both fine motor ability, i.e., producing hand movements, and visual-motor integration, i.e., tracing figures (see for instance fig. 3).

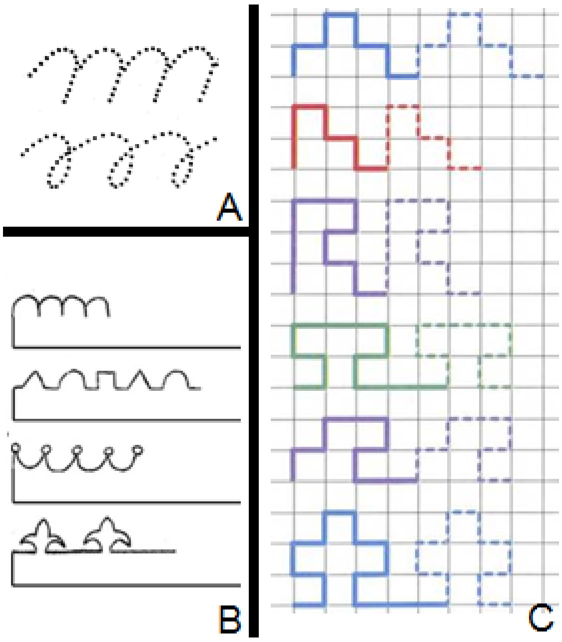

Figure 3. Examples of parts of writing pattern worksheets. The child is required to trace (A), finish (B) or trace and finish (C) the pattern.

In addition to possible roles of VMI and fine motor abilities, possible roles of kinaesthetic processing (proprioception), visual perception, sensory modalities and sustained attention have been suggested [22,36]. However, in a review of the literature no unambiguous evidence was found for associations of handwriting with these processes [36].

Handwriting interventions

In line with the discussed roles of fine motor- and VMI abilities in handwriting, and potentially of kinaesthetic-, visual-, and sensory processing, **sensorimotor interventions** target sensorimotor abilities. The literature suggests that these interventions are ineffective in improving handwriting [6,28,37,38]. For instance, kinaesthetic training sessions of one hour a day for six days did not result in improved handwriting [37]. In another study, children were trained four times a week for 30 minutes during five weeks. In this period children either practiced handwriting (therapeutic practice intervention) or visual, VMI, kinaesthetic and fine motor skills (sensorimotor intervention). As a result handwriting improved moderately in the therapeutic practice group, while it declined in the sensorimotor group. [38].

Task-oriented interventions are goal-directed and task-specific and are explicitly aimed at the motor processes that are relevant to learn writing [6]. Using this general approach, interventions in this category are aimed at letter form or prewriting movements [8,39]. In an intervention study, children produced letter forms in sessions that included imitation and self-evaluation. These sessions occurred 30 minutes a week for 10 weeks. Results of this study indicated that this task-oriented intervention was successful. [39] In another study, children were trained for three months in eighteen 30 minute sessions [8]. Training entailed exercises of prewriting abilities (fluent movements), fine motor abilities, and gross motor abilities. Components of training were selected based on results of individual assessment. This training procedure resulted in improved handwriting, which remained even after 12 months. [8] The available literature indicates that task-oriented approaches, aiming at the motor process of handwriting are effective [e.g., 6,8,39].

Finally, it has been shown that **interventions that explicitly train handwriting** are effective in improving handwriting legibility in children with HWP. [e.g., 4,6,40,41]

Successful components of handwriting interventions

For selection of the handwriting software components, it is important to know which components of handwriting interventions contribute to successful handwriting legibility improvement. Firstly, when children learn to write a new symbol repeated exercise seems most successful [42]. Secondly, symbols that have been learned are best trained through random order exercise, as this increases retention and transfer of the learned skills [42]. Thirdly, children learn writing new letters best, when they perceive how the letter is formed

and exercise production (visual-motor exercise), because this was more effective than only viewing letter formation (visual exercise) or only copying a static letter (motor exercise). [43]. Finally, combining visual-motor exercise with memory retrieval is even more effective than visual-motor exercise, when letters are taught [44].

Minimal training duration that is required for successful handwriting intervention

The content is not the only important component of handwriting intervention, as it is also important to know the minimal duration that is required to successfully improve handwriting quality. Handwriting legibility was successfully improved when grade 2-4 children trained one hour per week for eight weeks [28]. These training sessions involved both letter forming and linguistic awareness exercises. Also, when letter writing exercises occurred 30 minutes per week for 10 weeks, handwriting legibility improved [39]. Thus, total training durations of 5 to 8 hours across 8 to 10 weeks seem sufficient to improve handwriting.

Required content of the training software

Based on the discussed literature it now becomes possible to define the content of the training software. Firstly, the training software should include **actual handwriting**, because there is such strong evidence that handwriting exercises improve handwriting legibility. Still, the training software must also contain **writing pattern (writing movement) exercises** (e.g. fig. 3), as the phase 3 study will specifically train children with HWP and underlying motor problems. The software will also include **random order exercise of letter production**, which will be trained by **actual letter production with visual cues and memory retrieval**. Finally, the software should include sufficient material **to train children 1 hour a week for 8 weeks**.

Methods

Software will either be selected or developed. This software will include handwriting exercise and handwriting pattern exercise (e.g., fig. 3). We will first describe examples of available software. These examples may be useful as samples or as components for the training software we will develop.

Examples of available software

One example of software that aims at letter writing exercise is Novoskript digital[7]. The software is meant for children in grades 1 to 3. The software provides playful exercises which show were the letter starts (green), pauses (orange) and ends (red). The exercises also involve actual tracking of letters. Novoskript software entails exercise of letters, numbers, and capital letters in cursive script, and it also includes exercises of letter connections. Another example of software is Juf in a Box[8]. Although Juf in a Box is meant for 4 to 7 year old children, children with HWP and underlying motor deficits may benefit from handwriting movement exercises. The Juf in a Box method is actually a game, in which children playfully exercise writing patterns. For both software examples there is the problem that software is expensive. Moreover, neither contain all required contents. Still, this software may be used as an example for software development.

However, there is also software that is called pdf-notes[9]. This free software allows a user to mark and draw in pdf-documents on the iPad. Using pdf versions of worksheets that help

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[7] http://boreaal.nl/producten/novoskript_digitaal/

[8] http://www.jufinabox.com/

[9] https://itunes.apple.com/us/app/pdf-notes-free-for-ipad-pdf/id391487223?mt=8#

children exercise handwriting movements (e.g., fig. 3) or actual letters, pdf-notes can be used to perform writing exercises on the iPad.

General content of the software

The software will be programmed for the x-y writing tablet. This will allow us to track the children's writing exercises and improvement. The writing tablet software will include practise material for eight 1 hour sessions. Exercises will occur in a structured manner, so that all children exercise handwriting in approximately similar ways. The first four exercise sessions will include 15 minutes of handwriting pattern exercise (HPE), 30 minutes of letter, letter connection and capital letter exercise (LETE) and 15 minutes of free writing to apply and solidify the exercised material in a more natural form (FWE). The last four exercise sessions will include 15 minutes of HPE, 15 minutes of LETE, and 30 minutes of FWE. The software will be programmed so that it sends kinematic and spatial data to the researchers after every session.

Handwriting pattern exercises

Handwriting pattern exercises will include exercise material that is sufficient for two hours (8 x 15 min). It may be possible to use pdf-notes or similar software to digitalize material of handwriting pattern worksheets (e.g., fig. 3). The included handwriting patterns will then be presented and executed in random order over all sessions.

Letter, capital letter, and letter connection exercises

Letter, capital letter and letter connection exercise items with visual cues (e.g., arrows) will be programmed. Novoskript may function as an example for letter programming.

In sessions 1 and 2 all lower case letters will be practiced, in sessions 3-5 all capital letters will be practiced, and in sessions 6-8 all letter connections will be exercised.

Each item that is practiced will first be shown with visual cues, then be written with visual cues, and then be written from memory one time. The next letter will be exercised in the same manner. But after writing the letter from memory, the child is asked to write the previous letter from memory. Thus, the sequence is:

$A^{\text{view}}>A^{\text{produce}}>A^{\text{memory}}>B^{\text{view}}>B^{\text{produce}}>B^{\text{memory}}>A^{\text{memory}}>C^{\text{view}}>C^{\text{produce}}>C^{\text{memory}}>B^{\text{memory}}>(\ldots)$

In this sequence A, B, and C can be any letter, letter connection or capital letter. However, first all letters of the alphabet or all included connections are exercised in random order. After all letters have been exercised, the program automatically produces the next random order of all items. When these items have been exercised, the program automatically produces the next random order, and this cycle goes on until the 15 or 30 minutes are finished (depends on session).

In order to keep the exercise process fun, small feedback movies or pictures that relate to the exercised letter will be included. This will also allow the training child to rest the hand.

Free writing exercises

Finally in the free writing sessions, children will perform free writing tasks. If they want they can write a letter to the researchers about how boring or nice the exercises are, about what they learned, and so on. Otherwise themes will be: write about your best friend, write about your family, write about your favourite teacher, write about your least favourite subject, write about your favourite animal, write about the most scary bug, write about your favourite sport or hobby, and write about your future job.

Relevance of phase 2

The relevance of developing software is clear. Firstly, no software is available yet that combines handwriting pattern exercises and specific exercise of handwriting in a structured manner. Secondly, no software is available yet that trains handwriting in a structured manner, as our software will. This is necessary, because structured handwriting exercise allows for similar training across participants. Similar training across subjects will allow us to study the neural correlates of handwriting interventions.

Phase 3 – neural correlates of writing interventions

Backgrounds

Although successful interventions of handwriting problems (HWP) have been developed, HWP still has a high prevalence (5-33%). Therefore, testing the effect of the newly developed exercise software on the neural correlates of handwriting in children with HWP longitudinally may prove very relevant. Through improved understanding of these neural correlates, insights in the components of handwriting training may increase. Based on these insights it may be possible to optimise current conventional treatment.

Neural correlates of handwriting

For the description of the neural correlates of handwriting we refer to the backgrounds of phase 1 of the project. It is important to briefly note though, that left-lateralized superior frontal area, M1, SM1, (pre-)SMA, ventral premotor cortex, superior parietal area, fusiform gyrus, thalamus and putamen and the right-lateralized anterior and posterior cerebellum are involved in handwriting of adults (see fig. 2) [25]. Additionally, research in children revealed more widespread writing-related brain activations than adults and possibly signs of incomplete development of brain lateralisation [26,27].

Neural correlates of motor learning, measured through rs-fMRI, t-fMRI and DTI

To our knowledge, no studies have regarded the neural correlates of training in handwriting. Still, studies of motor learning may provide insight in which brain areas may be sensitive to change after training and how long participants should be trained before the neural correlates change. We will briefly discuss the results of a number of neuroimaging studies, which include t-fMRI, rs-fMRI and DTI studies.

With regards to t-fMRI, we will discuss three studies that investigated effects of motor learning on brain activity [45,46,47]. Firstly, alterations in ankle-movement related brain activity were found after tango lessons of one hour per day for five days. The altered brain activity included bilateral SMA, bilateral IPL, left primary somatosensory cortex, bilateral premotor cortex, right putamen, and in the left cerebellum posterior areas, dentate nucleus and vermis. [45] Additionally, one hour of tongue movement exercises induced alteration in tongue-related brain activity in motor-related areas, including bilateral M1, right SMA, bilateral putamen and bilateral cerebellum [46]. Finally, Parsons et al. [47] taught their participants to type a letter sequence on a novel keyboard. In a first fMRI session, comparisons across 48 minutes in which 192 letter sequences were typed revealed learning-related changes of activity in left cingulate areas, and in bilateral frontal, sensorimotor, parietal, temporal, occipital and cerebellar regions. Then participants received 18 minutes of typing training per day for five days, which resulted in altered activation in left frontal, left sensorimotor, bilateral parietal, bilateral temporoparietal, bilateral basal ganglia, left occipital, left cerebellar, right frontal, and right thalamus regions.

Motor-learning related functional connectivity was researched with training durations of 11 minutes to 8 weeks. During training, abilities like motor adaptation to chopstick use with the nondominant hand and changed joystick-cursor relationships were trained. [45,48,49] Such training regimens resulted in altered functional connectivity between:

- frontal and frontal areas [45,48];
- frontal and parietal areas [45,48,49];
- frontal and temporal areas [48];
- frontal and cerebellar areas [45,48];

- parietal and temporal areas [48];
- parietal and hippocampal areas [48];
- parietal and cerebellar areas [48,49];
- cerebellar and brainstem areas [48]

Thus, functional connectivity changes have been found to be induced by motor training in, e.g., fronto-cerebellar, parieto-cerebellar and fronto-parietal connections.

Finally, in four DTI studies participants were trained for one to six weeks [50,51,52,53]. Such short training regimens already induced changes in white matter tract integrity (measured through FA and MD). These changes were found in the tracts underlying the left superior frontal cortex, left M1, right cerebellum, right MFG, and right posterior IPS [50,51,52]. Additionally, altered white matter density was found in the white matter tracts connecting the cortex with the thalamus/putamen, the sensorimotor areas (SM) with the spinal cord and the left SM with the right SM [53]. Moreover, associations between motor skills and white matter density were found in the tracts underlying left prefrontal areas, right IPL, right superior temporal areas, left superior orbitofrontal cortex, and left M1 [50,52]. Associations with trained motor skills were also found in the right anterior limb of the internal capsule, the bilateral anterior centrum semiovale, the left brain stem, and the body of the corpus callosum [53]. Finally, Taubert et al. [52] found correlations between altered connectivity and muscular imbalances in the white matter underlying left superior parietal areas, right occipital areas, left cingulate gyrus, and bilateral cerebellum.

Summary of motor training data

In summary, DTI, rs-fMRI and t-fMRI studies revealed that changes in structural connectivity, functional connectivity and task-related brain activity can respectively be induced by 1 to 6 weeks, 11 minutes to 8 weeks, and 1 to 5 days of training. The changes occurred in part of the (connections underlying) areas that were also found to be involved in handwriting. Hence, it seems plausible that a training regimen of 8 weeks should be sufficient to induce changes in the rs-fMRI, t-fMRI and DTI signals.

Research question

The research question for the intervention study will be: “**what is the influence of the handwriting software developed in phase 2 on neural activity and connectivity, and how is this associated with improved handwriting skills?**”

Methods

Subjects

For the training study we will test 40 grade 2-4 children with HWP. Of these children 20 will be trained using the handwriting software and 20 will not be trained. We will recruit our subjects by offering a training program to 20 physiotherapists (10 per year). In exchange for the program, we will ask physiotherapists to recruit two children with HWP with underlying motor problems that are matched on age and gender.

General procedure

From each matched pair recruited by the physiotherapists, one child will be included in the training group and one child will be included in the no training (control) group.

In the training group, MRI scanning sessions will take place before and after training. After the first scanning session, training group children will start using the software developed in phase 2 to exercise their handwriting at home on a writing tablet. They will train their abilities for one hour per week during eight weeks, and every week on the same day. The second MRI scanning session will be planned 3 to 7 days after the last training session.

As far as possible the first and second scanning sessions of the control children will be matched in timing and inter-session duration with those of the training group children.

The scanning sessions will be the same as those described for the phase 1 study.

Scanning sessions

During each scanning session, both behavioural and neural assessments will take place. Behavioural assessment will measure the variables that will be found to be most consistently associated with neural correlates in phase 1. If all variables of handwriting and VMI consistently correlate with brain activity and connectivity, the sessions will be the same as the sessions described in phase 1 of the study. Hence, behavioural assessment will maximally take 30 minutes.

Neural assessments will involve sMRI, t-fMRI, rs-fMRI, and DTI scans that will be performed in the same manner as in phase 1 of the study. This means that neural scanning will take 60.5 minutes. Hence, total duration of each scanning session will be ± 1.5 hours.

Data analysis

The data will be preprocessed and analysed in the same manner as in the phase 1 study. The resulting variables of brain activity and connectivity and of handwriting skills will be evaluated in three ways. Firstly, we will evaluate whether training in handwriting improves handwriting skills. Secondly, we will test how training affects brain connectivity in the training group. Thirdly, we will evaluate whether improved handwriting skills can be associated with altered brain activity.

We will additionally track improvement in handwriting as children train their abilities. With that purpose, we will use DTW to measure letter form variability of the letters produced in the LETE part of each second session. We will also calculate absolute and relative power of velocity peaks in the 5-10 Hz spectrum using PSDA, and SNvpd over the letter production exercises in all sessions. This will be done to track how handwriting quality and fluency develops.

Use of experience from the phase 1 study

Were applicable, the experience of the phase 1 study with respect to optimisation of scanning procedures and behavioural measurements will be used in this phase of the study.

Relevance of phase 3

In this phase of the experiment, the following research question will be answered: “what is the influence of the handwriting software developed in phase 2 on neural activity and connectivity, and how is this associated with improved handwriting skills?”

Answering this research question is relevant because gaining insight in the neural underpinnings of handwriting training will potentially lead to a better understanding of the components of handwriting. Insight in these components and neural correlates of handwriting intervention may ultimately lead to new ways to train handwriting or to optimise handwriting interventions.

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