Evidence of Neural Recruitment in fMRI

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István Ákos Mórocz, M.D.

Doktori értekezés

Prof. Kovács Ilona, Ph.D., tanszékvezető

Boston, Massachusetts, U.S.A., 2009

to my parents

who educated me

and

to my enduring son

A notion can last for seconds or be as ephemeral as an eye blink. Experience shapes human cognition and enlists myriad neural phenomena which the mind orchestrates with meticulous accuracy. Rapid imaging will shed light on this enigmatic complexity of inner mental workings.

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Kivonat

Jelen doktori értekezés a humán agyi képalkotó eljárások módszertanáról szól, amely alapvető hatású a funkcionális mágneses rezonancia vizsgálat (fMRI) alapú kognitív agyi térképezés esetében. Az első részben bemutatok négy publikált értekezés témát, majd alaposan ismertetem a képalkotó mérés és elemzés során választott kísérleti paradigmát és fMRI technikát. A tanulmányok résztvevői egészséges személyek, zenére kiváltott epilepsziával élők, fejlődési diszkaluliával és skizofren személyiség zavarral élők voltak. A vizsgálat feladata zenehallgatás, gyorsított szó és mondat olvasás, újonnan tanult karakterekkel írt szavak megjegyzése és olvasása, és eltérő hangok detektálása volt. A paradigmák típusai a lassú blokk dizájntól a gyors esemény alapú dizájnig terjedtek. Az adatszerzés különböző sebességű 2D többszeletes és 3D képalkotó eljárásokra támaszkodott. Az adatelemzés a szokványos általános lineáris modell keretre épült az fMRI jel és modell korrelációjára alapozva. A kapott aktivációs térképek megbízható aktivációs pontokat mutattak, a különféle inger anyagoknak és a kognitív követelményeknek megfelelően a frontális, parietális, temporális és okcipitális régiókban. Mindazonáltal a megjelenő térképek túlegyszerüsítőek a kapcsolódó mentális feldolgozás komplexitásának fényében. Továbbá a hagyományos aktivációs pontok éles ellentétben állnak az emberi gondolkodás folyamatának élénkségéről alkotott tudásunkkal, ahogyan arra az elektrofiziológiai mérések is rámutatnak. Ezt a logikát követve a lassú fMRI szkennelési sebesség bizonyul a kognitív képalkotás legfőbb korlátának. A második részben összegyűjtöttem azokat az elveket, amelyek összhangban vannak a paradigma dizájn, az új szkenner technológiák és az elemzési módszerek kölcsönös együttműködésével, amelyben mindezek az fMRI módszer láncolatának összetevői. Ezek a módszerek lényegében a neuro-vaszkuláris válaszból adódó BOLD jel sajátos téri és idői információ mélyére hatolnak. A végső célunk a gondolkodási folyamat során többszörös fókuszú, ám hierarchikus kaszkádként felépülő idegi folyamatokról alkotott ismeretek gazdagítása. Az aktivációs pályák pontos leírása és az idői felbontású funkcionális kapcsolatok elősegítik az egészséges és patológiás dinamikus agyi állapot mintázatok megkülönböztetését, és általánosabb perspektívában körvonalazhatják az emberi megismerés idegi hálózatát.

Abstract

This PhD thesis is about methodologies applied in human brain imaging with profound impact on cognitive brain mapping using functional magnetic resonance imaging (fMRI). In a first part I present four published thesis topics and scrutinize thereafter the experimental paradigm chosen and the fMRI techniques applied during image acquisition and analysis. The studies included healthy participants and subjects with neurological conditions such as musicogenic epilepsy, developmental dyslexia or schizotypal personality disorder. The tasks performed were listening to music, accelerated reading of words and sentences, learning, memorizing and reading of a new alphabetic script, and listening to mismatch tones. Paradigm types spanned from slow block–design to the agile event–related design. Data acquisition relied on 2D multi–slice and 3D imaging techniques at various speeds. Data analysis comprised of customary correlation of the fMRI signal with model curves in a general linear model framework. The resulting activation maps comprehended solid foci, corresponding to the heterogeneous stimulus material and the variety of cognitive demands, in regions of frontal, parietal, temporal and occipital lobes. Nevertheless, the maps appeared in view of the complexity of the associated mental processes as oversimplified reflections thereof. Moreover, the static quality of the traditional activation blobs were in stark contrast with our understanding of the liveliness of human thought processes as implied by electrophysiological measures. Following this logic the slow data acquisition rate in fMRI proved as the single–most inimical limitation to cognitive imaging. In a second part I summoned principles that harmonize the synergistic interplay between paradigm design, novel scanner technology and analysis method where these are all links that belong to a long chain of fMRI methods. These methods shall in essence fathom out optimally both spatial and temporal information that is intrinsic to the BOLD fMRI signal secondary to a neuro–vascular response. Our ultimate goal is to enhance knowledge about the multi–focal but hierarchic cascade of neural recruitment in a thought process. An exact description of activation trajectories and time–resolved functional connectivity will then facilitate in distinguishing healthy from aberrant pathological patterns of dynamic brain states, and in a more general perspective, in delineating the neural circuitry of human cognition.

Expression of Thanks

Herewith I would like to express my greatest and most sincere gratitude to my mentors and colleagues who made it possible for me to apply for this Ph. D. program and ultimately under their caring guidance to arrive at the stage of handing in this thesis in the spring of this year 2009. I would like to mention here, in the order we interacted during this long process, the Professors: **Ferenc András Jólesz** at Harvard Medical School in Boston, USA; Drs. **Ilona Kovács** and **Csaba Pléh** at the Department of Cognitive Science, University of Technology & Economics in Budapest, Hungary; and Dr. **Balázs Gulyás** at the Department of Clinical Neuroscience, Karolinska Institute in Stockholm, Sweden.

Jegyzőkönyv

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Nyilatkozat

Alulírott Mórocz István Ákos kijelentem, hogy ezt a doktori értekezést magam készítettem és abban csak a megadott forrásokat használtam fel. Minden olyan részt, amelyet szó szerint, vagy azonos tartalomban, de átfogalmazva más forrásbol átvettem, egyértelműen, a forrás megadásával megjelöltem.

Boston, July 7, 2009

István Ákos Mórocz, M. D.

List of Abbreviations

DC	Developmental Dyscalculia
DL	Developmental Dyslexia
EEG	Electro–Encephalogram
FIR	Finite Impulse Response Function
fMRI	functional MRI
GLM	General Linear Model
IPS	Intra–Parietal Sulcus
IFG	Inferior Frontal Gyrus
ITI	Inter-Trial Interval
HRF	Hæmodynamic Response Function
MEG	Magneto–Encephalogram
MRI	Magnetic Resonance Imaging
PET	Positron Emission Tomography
PPC	Posterior Parietal Cortex
ROI	Region of Interest
SPD	Schizotypal Personality Disorder
TR	Time of Repetition

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Introduction

Neural activation and imaging

A device as complex as the human brain will at any given point in time reckon in the vast majority of areas that are available in its computing substrate. These areas interconnect locally, regionally and remotely via axonal pathways in the white matter, but other lesser known or even unknown cellular, physiological, physical and chemical mechanisms likely contribute further to the functioning of this machinery. For example, more recent evidence let us reconsider the role of inter–neural (neuronal and glial) mammal gap–junctions as they may have a far greater relevance for hyperfast electrical inter–cellular information processing than thought before[53]. Cortical and subcortical processes are observed to work in oscillation and synchronicity[4]. Much effort is made to characterize these re-occurring waves in various frequency bands, in order to decipher lastly the correlation of such higher-order electrical phenomena with measurements obtainable with current apparatus[30,41]. One may assume that the numerous detectable neural engagements related to a given action - be it rest, sleep, survival, reproduction, nutrition, schooling, learning, entertainment and so forth - are orchestrated as serial and parallel arrangements of each other influencing processes. Although magneto–electrical techniques like EEG or MEG offer the necessary speed for obtaining such temporally resolved information, their poor spatial resolution and localization uncertainty hampers computing of anatomically detailed activation road–maps. The opposite is true for current functional tomographic techniques like PET, fMRI and SPECT which apparently reveal readily regions of differential activation, but unfortunately seem hopelessly slow for extracting irregularities from dynamic activation trees. Because the temporal resolution of such tomographic measures does not come remotely close to the frequency at which the mentioned phenomena operate, no data can be obtained which would sufficiently isolate observations within the evoked neural activation cascades in order to differentiate between distinct subjects or populations.

Now, this is all true if we take for granted - erroneously - the short–lived duration of cellular responses, typically in the range of milliseconds, as the principal unit for comparing subjects. But there is a maturing agreement in the community that the

signal changes, we are interested in verifying through imaging, correspond to rather long episodes of up to several seconds of coherent oscillatory bursts within neural networks[51,52] which mirror focal brain activations following cognitive enrollment. The fluctuating oxygenation rate in the local capillary bed appears to reflect with enough fidelity the metabolic demand of the underlying oscillating neural system (Fig. 1)[30,32,41].
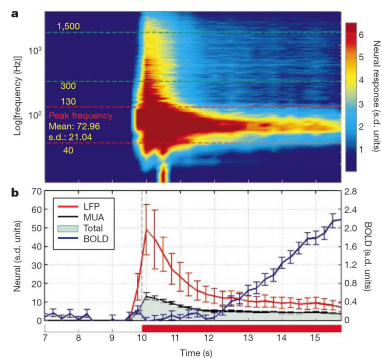
Fig. 1 Correspondence is shown between fMRI BOLD signal and field potential measures in the primate visual cortex. Gamma frequency demonstrates best temporal correlation with BOLD effect.[30]
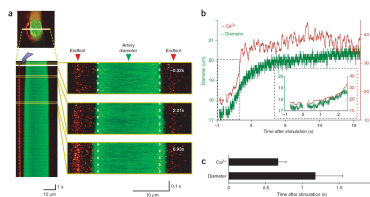
Fig. 2 Astrocytes trigger rapidly in the subsecond range a vasolidation (see green diameter) of the arteriol vessel, equipped with smooth muscle walls, following a neural stimulation.[54]
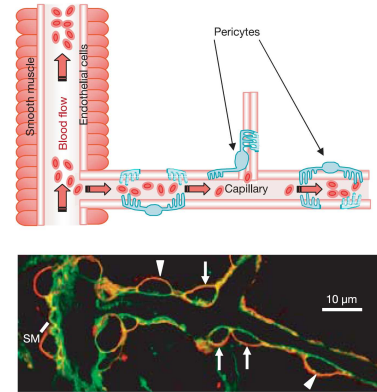
Fig. 3 Capillaries are capable of regulating their vessel diameter rapidly, and therefore are in the position to herald via the BOLD contrast mechanism swiftly neural activity that occur in neighbouring neuronal cells.[44]

Taking this all together, it appears that a successful segregation of interwoven activation sequences becomes a increasingly viable option for BOLD sensitized fMRI studies under state–of–the–art experimental conditions, in as much as the temporal discrepancy between neural network traffic and imaging sampling rate continues to narrow. One prerequisite, as discussed below, is to bypass the timing inconsistency between tomographic slices which is achieved by applying three-dimensional image acquisition schemes[28].[†] An additional benefit in using 3D techniques resides in the fact that signal contrasts from large venous vessels tend to be diminished, especially in combination with shifted–echo techniques[18] and the strong magnetic field gradients applied, while the signal from slow flowing blood in capillary beds is more likely to survive. Indeed, this signal is thought to represent more faithfully brain activity in that its proximity to a neural generator is immediate (Fig. 2–3)[44,54]. Moreover, no funnel effect will take place in capillaries like it happens in the case of venules and veins that collect blood from an ever growing area of numerous, necessarily both active and 'idle' brain regions.

[†]This is true to the extent that the order MR data is added to a 3D k–space matrix also affects the temporal independence of slices in the time domain.

fMRI techniques

Echo–Planar Imaging

MRI machines are highly flexible tools and offer a great variety of imaging modalities which permit in a given case to fine-tune not only settings of machine parameters but even the types of pulse sequences used which differ in fundamental physical properties. The principal acquisition technique applied nowadays in functional neuroimaging is T_2^* or BOLD sensitized two–dimensional echo–planar imaging (EPI). Importantly, 2D EPI collects rather rapidly, usually on a single–shot basis within a few dozens of ms, the entire k–space data matrix for a given slice whereas the slice–to–slice intervals are in the range of hundred to hundreds of ms (*volume repetition time (TR) / number of slices*). An outermost important factor to bear in mind is the order of slice acquisition in a stack of slices, which is usually done in an interleaved fashion, though slices sometimes get acquired serially. The main consequence for neuroimaging is that in 2D EPI, where by default a long series of stacks of two–dimensional slices (brain volumes) is collected, a time discrepancy is created between slices which introduces a serious artifact we have to account for during data analysis. This plays a painful role as soon as spatial and temporal manipulation on the data is performed in the framework of the usual preprocessing maneuvers, such as motion correction and smoothing, that instantly intermingle signal intensities among voxels from neighbouring slices with temporal incoherence. For that reason new algorithms were developed that correct for temporal deviation within a stack of slices in order to augment temporal correspondence between slices, optimally for a selected stack level, which often will be at the height of an area of interest. Unfortunately, the accuracy of timing correction decreases with distance from the chosen center time. The consequence of this slice timing problem is that an accurate temporal comparison among focal activations, that are located in different stack levels, is significantly hampered. It will interfere with the needs for the computation of hierarchic maps about neural activation cascades in terms of temporal accuracy and data quality. This problem was not so relevant in the past, because activation differences between paradigms or subjects were interpreted under the assumption that inferences are drawn from quasi 'static' metabolic states that are frozen in time and occur all at once within an event

or block of a given study paradigm. But today, as data acquisition techniques become faster, the slice timing problem will turn out detrimental if the purpose of the fMRI experiment is the study of temporally resolved hierarchic road–maps of event–related neural engagement.
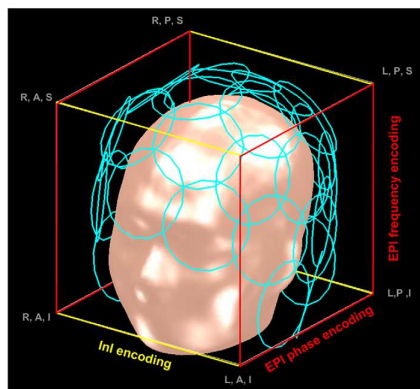
Fig. 4 EVI: The 3D InI spatial encoding scheme implemented using a high–density 32-channel array of coils. [28]
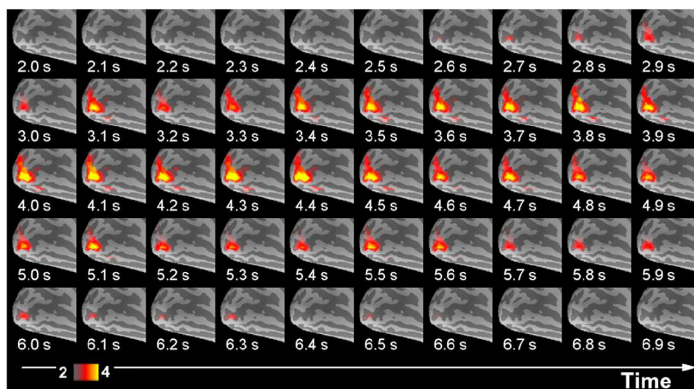
Fig. 5 EVI: Succession of single frames of the InI dSPM t–values in visual cortex averaged across five participants. Temporal interval between frames was kept at 100 ms. [28]

Rapid 3D volume acquisition techniques

A stack of image slices can be acquired as a true three-dimensional slab where total acquisition time per volume corresponds to number of slices $\times$ the time needed for one slice. By doing so, however, one collects the data for the entire 3D stack in one k–space matrix which nulls the slice timing differences during raw data reconstruction. The acquisition of an entire 3D data slab takes time and is done usually in multi–shot mode. Clever tricks like an shifted–echo acquisition scheme[55] that avoids sequence dead–time following the radio–frequency deposition pulse help shorten volume acquisition time without altering the optimal echo–time (TE) of approximately 30 ms at 3 Tesla B_0 field strength. A prominent implementation of this principle is called the PRESTO pulse sequence[17,40,55], and is in fact the fastest multi–shot imaging technique available, used for example in cardiac and functional MRI. Its real advantage comes into play when parallel imaging using multi–coil RF arrays and multi–channel RF receiver systems (Fig. 4) dramatically accelerates k–space acquisition times. It requires the knowledge of coil specific field density maps and the implementation of appropriate reconstruction algorithms[8,17,26]. Further speed-ups are achieved by the many recently developed subsampling techniques that collect only parts of the 3D k–space data (SPACE-RIP[27], partial–Fourier techniques, SENSE[17], UNFOLD[31], compressed sensing[15] and more) which can lead to a consider-

able shortening of the acquisition time per (brain) volume. The ultimate solutions in fast fMRI are currently single–shot 3D techniques like EVI that acquire full–brain data sets in a fraction of a second (Fig. 5 on page 4), albeit at lower resolution and using projection inverse reconstruction methods[28,45], and other approaches that base on the OVOC principle (one-voxel-one-coil)[22].

Analysis of the BOLD signal in neural networks

HRF based analysis

The analysis of imaging signal data sets for the study of the inner workings of neural networks will require the development of non–traditional novel statistical tools different from those used nowadays for functional neuroimaging. In contrast, a conventional, but at the same time perhaps most powerful way to test for simple signal changes - we shall call here 'activations' secondary to stimulus triggers - is a hypothesis-driven correlation analysis where a model curve, convoluted with an input response function, is compared to the measured fMRI signal on a voxel–by–voxel basis[†]. This function, frequently a hemodynamic response function (HRF, composed of two gamma functions)[1], models for a fix period of time the hypothetical signal from a neural response, which indirectly corresponds to an accumulation or a depletion of oxygen in the local vasculature, depending on metabolic demand and blood flow regulation, respectively. The fairly extensive length of the observed period (modelled usually half a minute) is perhaps the main reason for its statistical power because a multitude of measured signal time points (scans) are considered and assessed in combination with efficient t or F tests. The general linear model (GLM) matrix accepts any number of regressors (contributing contrasts) and thus provides the possibility of interesting linear combinations of effects, while the unexplained portion of the signal remains in a separate column, a 'waste basket' for unknown effects and noise. The HRF based analysis offers to a limited extent temporal flexibility (dispersion in time) for the convolution of the stimulus onset vector which should help to account for temporal inconsistencies of the BOLD response due to many not well understood variables such as flow velocity, local neuro–vascular coupling

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[†]Further information and references about analysis of fMRI data and HRF can be found under http://www.fil.ion.ucl.ac.uk/spm/ and under http://www.mrc-cbu.cam.ac.uk/.

effects, modulation of response - just to name a few. A fundamental limitation of the HRF method, however, is its weak sensitivity for the relative and absolute temporal engagement of focal contrasts of interest which renders our ambition futile in computing, based on ordering principles, hierarchic and temporally resolved activation maps.

FIR analysis

The *F*inite *I*mpulse *R*esponse (FIR) function offers the advantage of both to assess and to present the resulting activation maps at a finer grained temporal resolution - which evidently depends directly on the acquisition frequency - and to be still a hypothesis driven method, while at the same time to be entirely assumption–free regarding the temporal characteristics of the shape of the neural responses. In fact, if data sampling time is distinctly shorter than stimulus period and the related neuro–vascular response, then one can expect to obtain with the FIR method quite detailed and temporally fairly accurate trains of FIR bins with distinctly modulated areas on a bin–by–bin basis (Fig. 10 on page 102). The temporal sensitivity and specificity of the FIR method (and, ultimately, of any fMRI technique) may be enhanced *i*) by decoupling frequency and phase of both stimulus presentation and data acquisition, *ii*) by jittering stimulus onset times, *iii*) by averaging across event homologues ,and *iv*) by the inclusion of parametric features in the presented stimulus material.

Assumption-free analysis

A fundamentally different approach is to apply assumption-free methods where signal characteristics intrinsic to the data determine outcome of the analysis. A prominent candidate, the *I*ndependent *C*omponent *A*nalysis (ICA) of the voxel BOLD signal time course, produces components with temporal and anatomical distribution maps for maximally independent signal properties that may be shared across voxels or clusters.[†] The method may detect unexpected, unpredictable or otherwise even indeterminable event features that lead to synchronous signal modulation among neural structures like for example while watching film movies[19] or during prolonged periods of rest (brain 'default–

[†]ICA software: MELODIC http://www.fmrib.ox.ac.uk/fsl/melodic/index.html is a built-in functionality in the FSL package. GIFT is a toolbox http://icatb.sourceforge.net as part of the SPM5 software suite http://www.fil.ion.ucl.ac.uk/spm/

mode' or 'resting–state' network)[3,16,33]. Moreover, ICA may well serve for separating the fMRI signal time course from noise of unknown origin, and it offers the possibility to generate 'interesting regions' to be used as 'seed points' for advanced analysis procedures like the assessment of functional connectivity.

I will address analysis concepts once again in the discussion part of this thesis (page 101) as they introduce potentially quite distinct philosophies when interpreting the recorded patterns of neural responses. In this respect it is likely that in the near future machine learning algorithms and multivariate pattern classifiers will in parts supersede the traditional region and voxel–based understanding of the BOLD response and will instead introduce a new view on the brain's reaction in form of temporo–spatial finger-prints of brain states where then the presumptions about a neuro–vascular coupling may not play such a detrimental and outcome influencing role during the analysis [20,21,34,42]. On the other hand, I will also emphasize the crucial importance of a well tailored and synergistic interplay between paradigm design and the chosen analysis strategy (page 100). Only by optimally combining the three principle columns in the cognitive imaging pipeline, i.e., fMRI scanner methods, paradigm design and data analysis strategy, can one hope and expect to arrive at an intelligent, meaningful and worthy result from the neuroimaging apparatus. Such a valuable output shall mirror - desirably - hierarchically organized functional road–maps of neural recruitment as a consequence of a cognitive thought process.

Rational for Theses

I included four theses that shape the main scope of this work where various fMRI techniques were used as the principle measure for characterizing metabolic effects in cognition and for functional brain mapping. The aim is to compile my experiences I gained from these four theses and to share them here with the community. I will be pre-senting these theses in the following *four chapters* in form of former fMRI publications I contributed to as investigator over the last few years (Theses **I - IV**, on pages 15, 23, 49 and 77, respectively). *Compilation of Theses* thereafter (page 8) shall depict in greater detail my present view about these former publications, and outline potential enhance-ments in experimental design and setup that I believe the given studies in question may

have had profited from.

I bundled up these four theses since they share one common quality : It is the definite temporal rift between the expected swiftness of brain responses and the sampling rate their brain data was acquired at. It is the relative under–sampling thereof that is the common undesired denominator among the four theses. This under–sampling is also the principal point of my discussion that raises by its very existence a flurry of daunting questions about the completeness of commonly computed brain activation maps - questions that evidently are not simple to address. Irrespective of the stimulus paradigm design - be it conservative block shaped or boldly modelling for stimulus events - it is this temporal discrepancy that shall persistently interfere with a full–fledged assessment of brain recruitment via the BOLD mechanism at its full potential. Not so much my own doubts about the realness of significant activation blobs deem highly vexing to me than two perpetually nagging observations: First it is the *relative* importance, position and functional role of such activation foci that remain entirely blurred and in the dark within the activation brain cascade they are part of and which is supposedly fairly expatiated in human thought processes in general. Second one shall relentlessly reason about the frequently modest mass of these reported few hot–spots and wonder about the relevancy of such skewed ratios in view of the bigness of the remaining so–delineated '*non*–active' brain areas. So, once again, an enhanced pace of the data acquisition machinery would on one hand expectedly sharpen our temporal feel about the observed activation cascade. On the other hand it would size up its aptitude for detecting more details within activation cascades and in this respect mirror more adequately the ever evolving effects of a brain response. Notwithstanding, my intention is not to discourage entirely the acquisition of neurocognitive studies through common fMRI technology : the four theses included below give ample opportunity to discuss potentially beneficial adjustments in paradigm design and analysis methods which I will discuss in the next section.

Compilation of Theses

I will argue in the following paragraphs briefly about established fMRI techniques that are going to be presented in the four theses in the later chapters of this work. The

two main points I will consistently focus on are the suitability of the statistical contrasts used, and the applicability of alternative techniques that potentially enhance the outcome of the functional maps about brain recruitment for the cognitive tasks in question. My goal is not to unrightly slam design and style of former experiments, where in those cases the achieved results are perfectly rightful, but it is my intention to summarize learned experience collected the hard way over the last few years with mainly one idea in mind : to maximize, through choosing the appropriate imaging and paradigm parameters, the quality and quantity of scientific information that is attributable to and deducible from a cognitive task in question. The single most relevant change in this respect is in my opinion an increase of the *imaging speed* during data acquisition - which would that way properly account for and come closer in the temporal sense to the expectedly swift dynamics of transient brain activations. By doing so I follow my constant desire in collecting the richest possible information about neural recruitment regarding its spatial and temporal content in as much as it can be expected from an fMRI study with a contrast principle based on the BOLD mechanism[*]. A first point I will address with my comments is the statistical contrast chosen in the publication (*e.g.*, a comparison between runs, blocks, events or within events[†]). A second point I will comment on, is the inference about the spatio–temporal characteristics of neural networks one may hope to elicit in view of the experimental setup used, and what features in a given paradigm design would have helped in this respect to enhance the validity of the uncovered activation patterns.

Thesis I Aurae in Musicogenic Epilepsy. *page 15*

This fMRI study was about the characterization of epileptic aurae, a neurological condition induced by prolonged exposure to the seizure invoking stimulus, a musical tune the patient was familiar with. The experiment was repeated 10 times while the subject reported an aura in five out of the 10 fMRI runs. The contrasts of question were aura *vs* non–aura runs, as well as seizure inducing music *vs* control music of similar type. The

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[*]BOLD : blood oxygen level dependent
[†]*within* events = a contrast mechanism, *intrinsic* to event and task

experimental design was, due to several restrictions, kept extremely simple: *i)* each run consisted of two conditions, an 'off' and an 'on' music, respectively, then a long pause to give the patient time for recovery; *ii)* each condition was 39 s, long enough in order to elicit the biological effect of music and the potential aurae; *iii)* scanner repetition time was 5 s while the maximum number of scans per run was only 16.

Impression In view of the simplistic design available at the time of this study and the unpredictable nature of epileptic phenomena it is surprising that focal signal changes related to aural experience were traceable, and that a left temporal focus was ferret out that likely is a correlate of the clinical EEG findings recorded from this very region. Indeed, this study would today - modern hardware provided - much profit from *faster* scanner repetition times and *longer* scans. One played then within a single fMRI run many more cycles of 'seizure music' and control music including pauses for recovery, and made this way the paradigm design statistically robuster. Importantly, data scanned at a high temporal rate offers more detail about the remarkably slow and supposedly cascadic onset of musical appreciation[48,49,57] as it evolves and advances in the orbitofrontal structures - till to the point when it reaches the seizure–inducing focal hot spot, which we believe sits in the right rhinocortex of this patient.

Thesis II	Reading Acceleration in Dyslexia.	*page 23*

This fMRI study is about the neurobiological basis of reading training and the beneficial effect of accelerated reading in subjects with developmental dyslexia. It was observed in earlier studies that reading improves to a certain extent ('automatizes') if visual word and sentence material are presented at a faster pace than the normal reading routine. Corresponding with the theory, *fast* presentation rates for reading *non-words* did not differentiate the two population groups. However, and perhaps contra–intuitively, *slow* presentation rates did, and stimulated in control subjects stronger the visual areas, while in dyslexic subjects a relative signal increase was shown for the left BROCA's area and operculum. This latter result is suggestive for an irregular pathway of the grapheme–to–phoneme conversion. Two blocks of the same stimulus type were contrasted to three

baseline blocks (all within the very same scan). The statistical comparison between stimulus types had to be done therefore *across* fMRI runs.

Impression   A traditional fMRI design using a few blocks of *one* condition per scan is inherently susceptible to numerous artefacts related to scanner, physiological and psychological noise due to drifts and oscillating (reoccurring) phenomena. Therefore it is not excluded in my opinion that also the *fast* reading condition could have differentiated the two groups of participants, as observed in the *slow* condition - if used in a more elaborate, *mixed* and *event-related* paradigm design with *longer* scan runs. It would cancel out the aforementioned artefacts. At the same time it could reveal a far richer activation pattern, and with that render a more realistic scenario about brain recruitment during reading even in developmental dyslexia. The more detail is obtained about a sequence of brain involvement, the more increases the likelihood to eventually pinpoint truly faulty trajectories in a tree of neural recruitment in this developmental learning disability.

Thesis III   Reading an Artificial Script.   *page 49*

This fMRI study is about a *Morse*–like scripting system and the associated neural structures that are invoked during learning and usage of this new script. Volunteer subjects were asked to study over months of training words written in this artificial language. One phoneme was represented by two discrete symbols. The *explicit* condition involved training with letter decoding instructions, the *implicit* only showed whole words without instructions, while the *arbitrary* condition presented non-sense words. In short, the left posterior inferior frontal gyrus (IFG, BROCA's area) showed greater response for novel words in the well-trained (explicit) condition. This effect was interpreted as evidence that this brain area plays a role in decoding letters, it does the more, the less familiar the stimuli, hence words, are.

Impression   This is a cognitive study where the effects of learning, memory and active usage of a newly learned scripting system were studied. The prime question of interest to

me is in what way are cortex and associated subcortical structures functionally connected and synchronized while solving such a tantalizing task. It is of great scientific, social and economical importance to characterize the process of scholastic learning of scripting systems and how it is achieved in healthy subjects in general. The SOA (stimulus onset asynchrony) in this study is relatively long and covers several brain volumes (TRs) which in principle permits to subdivide each event's time course into sub-portions of the task. Therefore it may be intriguing to extract more than just one HRF effect by using a series of onset time points in form of several onset vectors. Now, the commonly used HRF technique, *i.e.*, an input function convoluted with the 32 s extensively long HRF function, is ill-suited to answer such an intriguing question about the temporal sequestration of a signal time course. It revealed indeed only a few foci, for example in the left IFG area. An FIR-based analysis approach may separate the SOA time course into TR-sized FIR bins where a FIR bin corresponds in this study with a 3 s time period. But then again, 3 s are an eternity when compared to neural engagements that last from a few milliseconds to seconds. In sum, in order to extract maps of sequential neural recruitment, like in this scenario of complex cognitive involvement, it is an absolute necessity to get the data acquisition machinery work at a significantly *higher pace.*

Thesis IV Schizotypal Personality Disorder. *page 77*

This fMRI study was originally designed as a *block-design* experiment playing various acoustic stimuli in the MR scanner in order to investigate strategies of auditory processing in people with schizotypal personality disorder. Traditional GLM analysis in block design fashion did not reveal differential patterns of activation for blocks that contained 25% tone deviant *off*-stimuli. On the other hand, a *parametric event-related* analysis design verified the expected signal changes in both auditory cortices where the 'added-on' effect of pitch deviant tones elicited in people with SPD an overshoot of BOLD response. This was a striking and unexpected achievement considering the quite unfortunate ratio of a scanner repetition time at 2.5 s and an auditory stimulus repetition time of 300 ms. This success may be explained in that the parametrically convoluted 'wavy' BOLD model, detail–rich as set up with an ISI length of 300 ms, assumably fitted

the collected MR signal (and with that the physiology of the brain response) better than a simple block-based study design with flat tops in the HRF convoluted signal curve. No further brain areas were detected.

Impression   Again, like in the previous three studies, the outcome also of this study may have been considerably richer and multifaceted, had been the *acquisition frequency* of the fMRI data moved closer to the *high* stimulus presentation rate of the auditory tones. The aberrant activation response in subjects with schizotypal personality disorder, observed in the auditory brain areas using traditional techniques, are entirely valuable. Nevertheless, one may wonder why no further brain structures such as the cingulate and prefrontal areas were seen recruited upon processing of such unawaited startling events[7,47] like the presented pitch-deviant tones.

Anticipation on discussion

Under *Mental Processes* (page 99) I will present evidence from the literature and formulate simple principles for functional brain mapping with one cardinal goal in mind : to unveil cascades of neural recruitment that underlie cognitive thought processes and which are embedded in signal time–course patterns and are hence in principle deducible from the temporal and spatial spectra of fMRI data. I will address features about the study design, data acquisition and analysis, that in a synergistic manner shall enhance the experimental system's total sensitivity and specificity. *An ideal stimulus vector* (page 100), for example, carries for each event a specific set of characteristic features. *Three distinct analysis methods* (page 101) applied to an fMRI study about the neurobiology of mental arithmetic lead to discrete signal descriptors and elucidate the varying degree of temporal information that can be gained from a given analysis method. *Final notions* (page 103) conclude about the current technical advances to step up from today's semi–static imaging modalities to rather dynamic levels of functional brain mapping which shall open windows of new opportunities for cognitive neuroscience.

fMRI of triggerable aurae in musicogenic epilepsy[*]

Abstract

The authors studied a patient with musicogenic epilepsy triggered by one specific musical piece using 3D PRESTO fMRI. During epileptic aurae initiated by the stimulus, signal increases were found in the left anterior temporal lobe, correlating with ictal EEG and SPECT showing a left anterior temporal focus, and the right gyrus rectus. Because fMRI indicated a cascade of recruitment of the ventral frontal lobes by epileptogenic music, left anterior temporal lobe activity could be secondary to a right gyrus rectus focus, possibly triggered by emotional processing of music.

Introduction

Musicogenic epilepsy[1,2] is a rare medical condition generally classified as a specific stimulus-triggered (reflex) epilepsy. It is characterized by a long latency between stimulus exposure and seizure induction, frequently in the range of minutes. Musicogenic seizures involve temporal lobe structures[1,2] and are most frequently complex partial.

The uniqueness and specificity of the musical triggers include a wide range: the sound of particular church bells, the melody of the Marseillaise, the metallic character of a singer's voice, or the sound of a street vendor's flute, only at sunset.[1,2] In some cases the trigger for seizures was the actual performance of a specific musical piece on a given instrument. Emotional cofactors may contribute to the development of a brain state close to a threshold from which seizure activity may be initiated.[2]

Few studies have investigated the effects of epileptic activity on the fMRI signal in patients with spontaneous epileptic discharges.[3,4] Here we report an fMRI study in an individual with medically wellcontrolled musicogenic seizures where blood oxygenation level dependent (BOLD) signal changes were induced by epileptic aurae upon exposure to specific epileptogenic music.
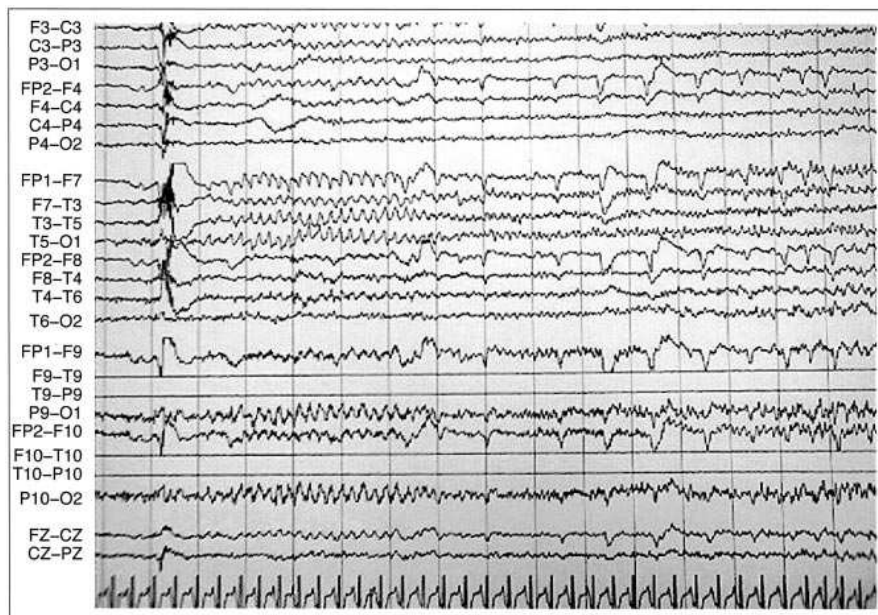
Fig. 1 EEG tracing acquired while the patient was exposed to the epileptogenic music. Left temporal seizure activity: a period of θ-rhythmic waves lasting 6 seconds was followed by discharges of lower voltage and higher frequency, which persisted through the end of the record. Electrode positions are indicated. Each gridline represents 1 second.

Materials and methods

Patient A 48-year-old right-handed woman had a history of music-induced "strange feelings" since age 41. Beginning at age 42, she had music-induced complex partial seizures. The musical triggers were one song performed by Whitney Houston and one by Boyz II Men. She underwent continuous EEG monitoring during which four episodes of musicogenic complex partial seizures (triggered by music by Boyz II Men) with a left anterior temporal focus were captured (figure 1). An ictal SPECT scan showed left temporal hyperperfusion; the interictal SPECT revealed mild hypoperfusion in the same area. Results on MRI studies and neurologic examination were normal. Medication included phenobarbital and Tegretol (Novartis, East Hanover, NJ).

Music tasks The tune "I believe in you and me" by Whitney Houston was selected as the trigger condition causing strong aurae feelings: pressure in the abdominal and then pectoral area, a "rushing" sensation, palpitations, and heart racing. A similar sounding song ("Somebody bigger than you and I" from the same album) served as control condition. Both tunes were played each time from the beginning of the track. The patient was instructed to press a response button at aura onset. Each of the 10 imaging sessions included 39 seconds of control music (8 scans) followed by 39 seconds (8 scans) of the epileptogenic music in a block design fashion. The patient was allowed to rest for a few minutes between sessions while her baseline pulse rate recovered, and she was examined for alertness and well being.

Imaging   T1-weighted spin-echo images using a 1.5 Tesla Philips (Eindhoven, the Netherlands) Gyroscan MRI scanner were acquired as anatomic reference; a version of the three-dimensional gradient-recalled shifted-echo PRESTO pulse sequence was used for functional studies.[5] PRESTO has the advantages of a soft, monotonous, noise level, good image quality with low image distortion rates (especially of the ventral brain surface), slice timing consistency, and inherently low susceptibility to blood inflow effects. In-plane resolution was 3.75×3.75 mm, slice thickness 3.5 mm, effective echo time 35 msec, repetition time (TR) 24 msec, flip angle 30°, and 5 echoes/TR. The acquisition time for 16 slices (one scan) was approximately 5 seconds. In each fMRI session, two dummy scans were discarded.

fMRI analysis   A total of 160 functional scans were spatially realigned, smoothed with a Gaussian filter of 10 mm, and coregistered with the anatomic scan using SPM99 (http://www.fil.ion. ucl.ac.uk/spm). A boxcar model was used to contrast epileptogenic vs control music conditions and aura vs nonaura sessions. All contrasts were examined with a voxelwise significance level of 0.05 (t-test) corrected for multiple comparisons across the brain volume. A separate small volume correction, taking into consideration the area of the left temporal lobe, was applied to the significance threshold for the assessment of the aura effect in the left anterior temporal lobe (laTL) (contrasting the epileptogenic music conditions during the aura vs nonaura sessions). Cluster size threshold was kept at zero voxels. The mean over all significant voxels in a given region of interest was determined using the time series of the realigned and smoothed data set as source.

A second, fundamentally different, model- and assumption-free method of analysis based on independent component analysis (ICA) was applied to decompose the time series into spatial and temporal components6 using the software program MELODIC (http://www.fmrib.ox.ac.uk/fsl/). Resulting activity maps were defined by the selected spatial component superimposed on anatomic slices whereas the corresponding temporal component was the source for the variance-normalized time course and representative for all voxels displayed.
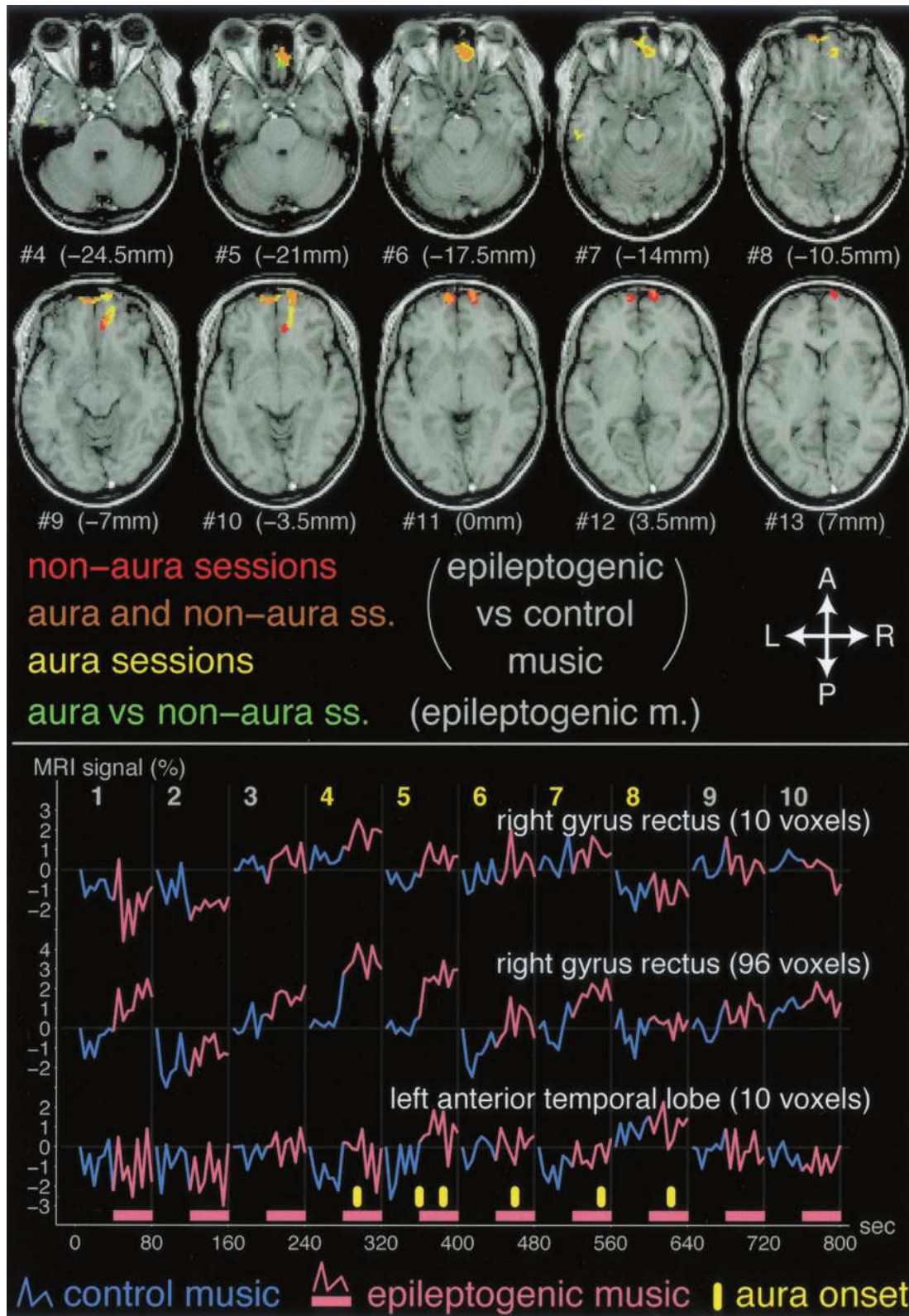
Fig. 2 fMRI activity maps for the epileptogenic music effect and for the aura effect superimposed on anatomic MRI slices (slice numbers and positions relative to anterior commissure/posterior commissure plane indicated). Red and yellow represent voxels with significant fMRI signal increase for the seizure music conditions: red in the nonaura sessions, yellow in the aura sessions. Orange voxels represent overlapping signal increases in both session types. Voxels in green in the rGR and the left anterior temporal lobe (laTL) demonstrate significantly higher fMRI signals during the epileptogenic music in the aura as compared to the nonaura sessions. Lower panels show the averaged fMRI signal time course: top, the 10 green voxels in the rGR; middle, the orange, yellow, and green voxels in the rGR; bottom, green and yellow laTL voxels. Blue curve = control music conditions; pink curve = seizure music conditions. Vertical yellow marks indicate aura onset report times.

Results

The patient reported an aura onset in 5 of 10 fMRI sessions (twice in the fifth session). Average response time for the first button press after initiation of the epileptogenic music was 23.6 seconds (SD_{n-1} 5.6 seconds, $n = 5$). No abnormal movements or adverse reactions were observed. Pulse rate increased from about 92 beats per minute (bpm) to 105 to 110 bpm toward the end of the control music conditions with maximum of 110 to 116 bpm reached by the end of the seizure triggering music conditions. Figure 2 shows the SPM99 comparison of the two music conditions (epileptogenic *vs* control music): signal increases were found in both aura sessions and nonaura sessions in the bilateral frontal poles, right anterior cingulate, and the right gyrus rectus (rGR), whereas signal decreases occurred bilaterally in the caudal GR and adjacent structures in the orbital and subcallosal cingular gyri (not shown). Differential activation for the aura sessions (during epileptogenic music) was evident in rGR and laTL. The raw fMRI signal time course (figure 2, lower panels) shows signal increases for the epileptogenic music in rGR during the first four aura sessions.
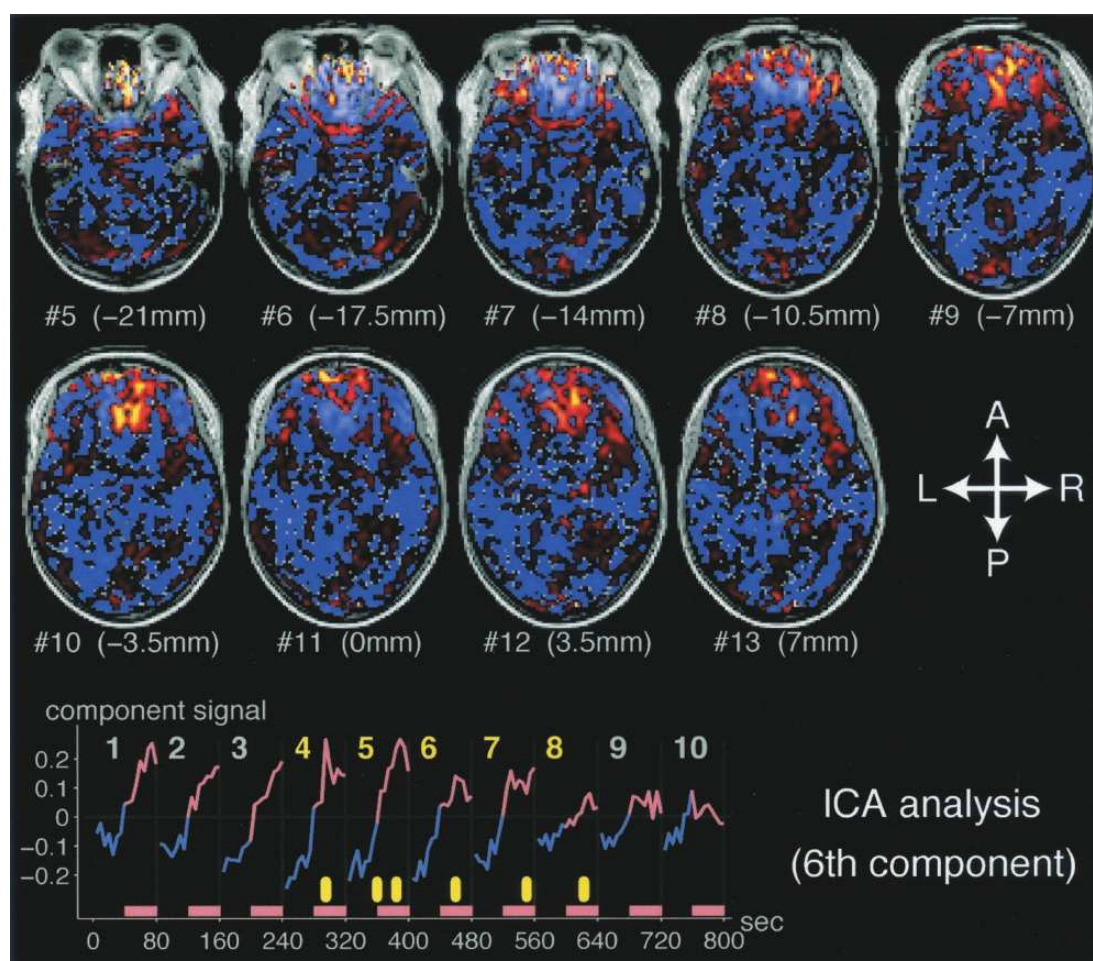
Fig. 3 fMRI activity maps show the spatial extent of the sixth component (selected for its frequency spectrum, best corresponding with stimulus paradigm) of the 10-dimensional independent component analysis. Voxels are rescaled with unit variance. Red to yellow represent voxels with increased component intensity whereas blue to light blue represent signal decreases. Lower panel = the time course for the corresponding temporal (variance-normalized) component; symbols and color coding as in figure 2.

Similar effects of music conditions in the frontal cortex were also found in the ICA analysis. Figure 3 depicts the spatial extent and time course of the ICA component best corresponding to the stimulus paradigm (frequency spectrum) in all 10 sessions. A comparison of the signal amplitudes in the two music conditions – control and epileptogenic – during the aura *vs* the nonaura sessions was significant (interaction between music × aura, general linear model-analysis of variance for repeated measures, F[1,7] = 20.97, $p < 0.0025$). Two mathematical control experiments tested for movementrelated artifacts in areas prone to susceptibility by movement artifacts. The inclusion of movement parameter estimates as covariates in the SPM99 design matrix and the application of the Unwarp technique[7] (http://www.fil.ion.ucl.ac.uk/spm/toolbox/unwarp.html) made no substantial difference in the analysis results.

Discussion

Repeated exposure to the unique seizure-triggering music resulted in two distinct patterns of consistent BOLD signal changes: one related to the actual triggering of musicogenic aurae, the other related to exposure to the specific epileptogenic music. The fMRI data and the ictal EEG and SPECT measurements indicated the laTL as a locus for seizure-related activity. However, the PRESTO fMRI measurements not only revealed additional foci in the ventral frontal lobes but also indicated that the rGR activation, occurring at an earlier phase of exposure to epileptogenic music, may have initiated the seizure cascade. This is supported by the finding that the laTL (not known to play any role in music processing) was not activated by seizure-music exposure per se, as the fronto-orbital lobes were. The fronto-orbital structures are believed to be key structures in processing emotional aspects of music.[2,8]

Fronto-orbital activation was found in a PET study[8] in which the effect of increasingly pleasant music was investigated. Lesion studies also support that emotional processing of music depends on the fronto-orbital brain.[9] The patient reported here expressed no interest in music in general, has never played a musical instrument, and had no particular memories or feelings related to the triggering pieces of music. However, her pulse measurements indicated that she was having an autonomic response even before being exposed to the epileptogenic music.

Because our experimental fMRI design was inherently sensitive to the effect of prolonged listening to music (control followed by epileptogenic music), the observed activity changes in the fronto-orbital lobes may have reflected emotional arousal and memory related to the music[1,2] rather than seizure activity per se. Our findings suggest that during the patient's aura, the main differential evoked activity was localized in the rGR. Nevertheless, the control music may have contributed to the enhancement of the patient"s susceptibility to the ensuing seizure-inducing music, possibly in the form of progressive cortical recruitment.[2] Indeed, the large negative activations that surrounded the rGR

in the epileptogenic music conditions may indicate uncompensated hypermetabolism or vascular dysregulation.[10]

Even within the relatively short time frame of the fMRI study, the ability of the same stimulus to evoke an epileptic aura varied. The imminent exposure to the feared stimulus and the foreign atmosphere of an fMRI experiment may have contributed to the failure to induce epileptic aurae in the first three exposures, whereas the results for the final two sessions are suggestive of habituation to the repeated stimulus presentation.[1,2] A similar habituation was found for the signal in the rGR during the aura sessions although a clear-cut correlation with the button press latencies was not evident.

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An fMRI study of the differential effects of word presentation rates (reading acceleration) on dyslexic readers' brain activity patterns*

Abstract

Several lines of evidence have recently provided a clear indication that word reading rate can be considered as an independent variable which influences comprehension as well as accuracy in reading. Thus, not only is fluent reading a critical characteristic of skilled (automatic) reading, it has been shown that faster reading does not necessarily incur a cost in terms of accuracy. Indeed, readers of various levels of reading proficiency, as well as clearly impaired readers (dyslexics), if made to read faster than their normal (routine) reading rate, can increase their decoding accuracy and comprehension. Using block design, blood-(de)oxygenation-level-dependent (BOLD) functional magnetic resonance imaging we studied the differences in brain activation patterns induced by reading and script processing in adult dyslexics and normal reading controls as a function of two word presentation rates. Word presentation rates were set individually for each participant to correspond to his/her routine reading rate (slow) and to a correspondingly faster rate (fast). Three task conditions were tested: sentences (plausibility judgment), single words (concrete/abstract judgment), non-words (homophonic judgment). Comprehension and accuracy in the faster presentation rates were unimpaired in both groups. There were no significant differences between the activation patterns induced in both groups in 'slow' reading of sentences and single words, but 'fast' reading was related to higher activations in visual areas in the normal readers. However, in the slow non-words condition the dyslexics were characterized by activations in the Lt IFG (Broca's area) and operculum, while the control readers clearly activated visual processing areas (extra-striate cortex). These differences in brain activation patterns were not found in the fast non-words condition. We propose that time-constrained (accelerated) script decoding may prompt the dyslexic brain to process graphemic information in a different manner compared to the one employed in unconstrained (routine) reading, in some conditions in a manner

of processing much closer to the one employed by normal reading controls.

1. Introduction

Developmental dyslexia has a high incidence (5-17%) among school-age children, occurs in most known languages and results in a considerable disability in literate societies because the reading deficits persist into adulthood (Shaywitz et al., 1998). A recent report on dyslexia and literacy (British Psychological Society (BPS), 1999) proposed the following working definition of developmental dyslexia: 'Dyslexia is evident when accurate and fluent word reading and/or spelling develops very incompletely or with great difficulty'. The Health Council of the Netherlands stresses the inability to attain 'automatization', i.e. effortless, fast and accurate word identification, in dyslexics. Thus, in the view of both these experts' panels, poor readers are characterized by non-fluent, slow and inaccurate word reading (Kame'enui, Simmons, Good, & Harn, 2001; Torgesen, 2000; Wolf, 2001; Wolf, Bowers, & Biddle, 2000).

The emphasis on both accuracy and fluency reflects several changes in the current understanding of dyslexia (see Wolf (2001) for review) including a change in the common perspective that reading fluency is a result of the effectiveness of phonological processing (Lyon & Moats, 1997). Given the notion that normal reading acquisition could be conceptualized as the acquisition of non-linguistic skills (Bitan & Karni, 2004; Karni & Bertini, 1997) one may consider the possibility that gains in speed and gains accuracy in the performance of a given task may represent different aspects of knowledge (Hikosaka et al., 2002). Indeed, an improvement in both speed and accuracy with practice, rather than speed accuracy tradeoff, is a recognized characteristic of skill acquisition (procedural learning) in both motor and perceptual domains (Karni, 1996; Karni et al., 1998) although there may be phase differences in the attainment of these two parameters of performance (Korman, Raz, Flash, & Karni, 2003). The notion that skilled reading evolves in a manner similar to the acquisition of non-linguistic skills further suggests that there may be qualitative differences in the way the reading task is accomplished at different levels of accumulated experience with reading (and specific lexical items)—i.e. that different levels of brain representations may sub-serve word recognition at different stages of experience (Bitan & Karni, 2003; Clark & Wagner, 2003; Ofen-Noy, Dudai, & Karni, 2003; Papagno, Valentine, & Baddeley, 1991; Turkeltaub, Gareau, Flowers, Zeffiro, & Eden, 2003; and see, for example, in non-linguistic, motor, tasks, Korman et al., 2003; Sosnik, Hauptmann, Karni, & Flash, 2004). The notion that similar basic neural mechanisms underlay the acquisition and retention of non-linguistic and linguistic skills (Bitan & Karni, 2003; Karni & Bertini, 1997) further suggests that the ability to employ skilled reading routines may be specific for, and thus critically dependent on, the task pertaining to the words being read (Bitan & Karni, 2004), and even on simple physical aspects of the script presentation such as word presentation rates. This latter

notion is in line with the proposal by Tallal and co-workers of a rather basic (low-level) multi-sensory processing deficit in dyslexia, whose core is difficulties in time-constraint perception, in dyslexics (Merzenich et al., 1996; Stein, 1991; Tallal, 1980; Tallal et al., 1996; Zeffiro & Eden, 2000).

There is growing support for the notion that word reading fluency may reflect subprocesses other than phonology and can thus be conceptualized as a separate factor for the reading deficit (Breznitz, 2002; Kame'enui et al., 2001; Wolf & Bowers, 2000). Recent data indicate the presence of a possible second core deficit (in addition to phonology) in dyslexia, measured as naming-speed deficits (Denkla & Rudel, 1976; Wolf, 1997, 1999; Wolf & Bowers, 2000; Wolf et al., 2000) and/or speed of processing deficits (Breznitz, 1997a,b, 2002) related to both fluency and comprehension problems. Some reading intervention studies have also indicated that while intensive training in phonemic awareness could improve decoding and word identification in poor readers, there were only minimal gains in reading fluency (Lyon & Moats, 1997; review see Meyer and Felton (1999)). Moreover, cross-linguistic data suggest that in languages with an irregular orthography, reading fluency poses the primary difficulty in regular orthographies (Wimmer & Mayringer, 2000; Wimmer, Mayringer, & Landerl, 1998). Experimental findings, from studies conducted in the last decade or so, have provided a clear indication that word reading rate can be considered as an independent variable which influences comprehension as well as accuracy in reading (Breznitz, 1997a,b, 2001, 2002).

Support for the notion of fluency as an independent parameter in reading has comes from the recently described, rather paradoxical, 'acceleration phenomenon' (Breznitz, 2001, 2002). The basic finding, in multiple experiments, was that native Hebrew, and native English, readers of various levels of reading ability, as well as clearly impaired readers (dyslexics), if made to read, about 10-20%, faster than their normal (routine) reading rate, increase their decoding accuracy and comprehension (Breznitz, 1997a,b, 2001, Breznitz, DeMarco, & Hakerem, 1993; Breznitz, DeMarco, Shammi, & Hakerem, 1994; Breznitz & Leiken, 2000; Breznitz & Share, 1992). The experimental set-up in all the above studies, constituted of a unique, and certainly unusual, script presentation method which constrained reading time: one in which the target script (words, sentences) was erased off the screen, letter by letter in the direction of reading, at a set rate. While the neurological substrates of this effect are not known, there are indications that the acceleration procedure can be conducive to extended attention span and reduced distractibility, as well as enabling the readers to surmount some of the limitations of shortterm memory (Breznitz, 1997b; Breznitz & Share, 1992). Several other cognitive mechanisms were proposed, including enhanced word retrieval from the mental lexicon, and there are some suggestions that the acceleration procedure enabled dyslexic children to partially surmount their phonological deficits (Breznitz, 1997a, 2002).

These data provided a basis for considering the proposition that accelerated reading

may prompt the dyslexic brain to process graphemic information in a different manner from the one engaged routinely (i.e. when no time constraints are induced by the script presentation system). It should be noted, however, that the degree to which dyslexics can use this alternative reading mode may be rather limited and depend on the very specific script presentation system described above. Initial support for the alternative reading mode conjecture was found in combined behavioral and electrophysiological (event related potentials, ERP) studies wherein sub-lexical (e.g. letters, visual patterns) and various lexical stimuli were presented to adult dyslexic and normal readers at different presentation times. These studies (Breznitz, 2002; Breznitz et al., 1993; Breznitz & Leiken, 2000; Leiken & Breznitz, 1999) showed that fast paced stimulus presentations resulted in significantly enhanced accuracy in both discrimination and recognition tasks in dyslexic readers. Moreover, in both normal reading and dyslexic individuals, ERP latencies (P200 and P300) were found to appear earlier in the fast as compared to the slow presentation condition. However, latency differences between the two presentation conditions were more pronounced in the dyslexic individuals. Surprisingly, the ERP components were spatially distributed in a differential manner in the two groups as a function of acceleration (Breznitz et al., 1993; Breznitz & Leiken, 2000; Leiken & Breznitz, 1999)

There is accumulating support for the notion that different routines for reading are employed in the dyslexics' as compared to normal readers' brains from recent studies using imaging techniques such as fMRI and PET (Shaywitz et al., 1997, 2003; Zeffiro & Eden, 2000). Several studies have specifically addressed the issue of brain regions that sub-serve the process of normal reading (Demonet, Price, Wise, & Frackowiak, 1994; Petersen & Fiez, 1993; for a recent review, see Zeffiro and Eden (2000)) and there are many indications that although differently selected participants, and different tasks, languages and reading materials, were studied in the different studies, dyslexic readers may rely on the engagement of different brain areas compared to normal readers, given the same task. One seminal study has suggested that dyslexic readers may exhibit a functional disruption in a broad system comprising the posterior cortex encompassing visual and language areas, as well as parts of the parietal association cortex (Shaywitz & Shaywitz, 1999) and may more heavily rely on left inferior frontal cortex compared to normal reading controls. Several studies have shown significant brain activity differences between dyslexic and normal readers while performing phonological and other script decoding tasks (Paulesu, Frith, Snowling, & Gallagher, 1996; Pugh et al., 2000; Shaywitz et al., 1998). Simos et al. (2002) have recently studied the brain activation patterns in the brains of dyslexic individuals using MEG measurements, before and after intensive training on phonological tasks. Their main findings were that before training the dyslexics' brains showed little or no activation in the posterior superior temporal gyrus (STGp) an area normally involved in phonological processing. However, after phono-

logical training, the activity in the STGp increased by several orders of magnitude in every dyslexic participant.

Although somewhat simplistic and in no way exhaustive or conclusive a possible summary of a number of different brain imaging studies is that compared to normal readers dyslexics display relatively less engagement of posterior visual and language regions and relatively more activation in anterior language regions when performing tasks that make progressively greater demands on phonological analysis (Paulesu et. al., 1996; Shaywitz et al., 1998; Zeffiro & Eden, 2000). One should note that most published studies were concerned with dyslexia in English which may be considered rather as an outlier orthography (Share, 2003) and also that most studies were concerned with adult dyslexics, mainly because of methodological complexities associated with developmental brain imaging studies wherein children must participate (Gaillard et al., 2001; Turkeltaub et al., 2003).

The current study was designed to investigate the conjectured possibility that time-constrained reading (acceleration) may enhance reading effectiveness among dyslexic readers by prompting the dyslexic brain to process graphemic information in a manner different from the one engaged routinely (i.e. when no time constraints are imposed by the script presentation system) in reading. The results suggest that while in some reading tasks the difference between the two reading groups became significant, a manner of script processing much closer to the one employed by normal reading controls was invoked, given time constraints, in a script decoding task, using non-lexical items, by well compensated adult dyslexics.

2. Methods

2.1. Participants   Male university students, 8 dyslexic and 8 age matched normal readers, participated in the study. The two groups were also matched on nonverbal IQ scores (Raven standard progressive matrices, Raven, 1960). All subjects were right handed with normal or corrected-to-normal vision and with no neurological deficiencies. The participants' ages ranged from 22 to 25 years (mean age 23 years and 5 months, SD=0.10). All were native Hebrew speakers and were paid for their time participating in the study. The dyslexic readers were recruited through the University Student Support Service of the University of Haifa having been diagnosed as dyslexic in childhood and found to be impaired readers by the Student Support Service.

Table 1 summarizes the main behavioral measures characterizing the two groups.

Behavioral baseline measures

Test	Control		Dyslexic		Group comparison
	Mean	SD	Mean	SD	$t(1, 15)$
Raven matrices (raw scores)	52.1	3.62	51.65	3.81	NS
Decoding, Z-scores (words, pseudo-words and connected text)	1.01	1.23	-1.52	1.66	3.03**
Reading time-connected text (in s)	81.12	15.3	101.1	30.01	2.61**
Comprehension connected text (out of 6)	5.69	1.34	5.01	1.71	NS
Phonological accuracy (out of 40)	37.3	3.09	24.2	15.87	3.90**
Phonological time (in s)	99.07	5.36	146.2	7.36	3.44**
Orthographic processing: parsing test—accuracy (out of 50)	48.72	2.94	36.77	4.07	3.73**
Orthographic processing: parsing test—time (in s)	167.91	5.23	276.84	23.16	3.23**
Working memory completion (out of 10)	5.67	0.56	4.33	0.75	3.21**
Working memory opposites (out of 10)	6.89	0.83	4.95	0.91	3.47**
Total word production fluency	47.81	5.43	33.65	6.43	3.32**
% WAIS digit symbols (percent accuracy)	100%	6.01	78%	8.65	3.63**
WISC-R symbol search (speed)	59.48	7.51	46.76	9.66	3.13**

Table. 1 $*p < 0.01, **p < 0.001$.

IQ was assessed using the Raven standard progressive matrices (Raven, 1960). Several tests were used to obtain estimates of reading accuracy, reading time and comprehension. *Decoding skills*: One Minute Tests (Shatil, 1997a,b). This battery included two subtests in which subjects were asked to read lists as quickly and accurately as possible within the space of 1 min. The first list contained 100 real words arranged in order of increasing length (1-5 syllables) and decreasing frequency, and the second list was comprised of 100 pseudo-words arranged in order of increasing length (1-5 syllables). Scores were based on the number of words and pseudo-words read correctly. In order to obtain a comprehensive decoding score, Z-scores were first calculated for each of the lists separately and then combined to give a total Z-score for decoding performance. *Reading comprehension, accuracy and speed in context*: the reading performance for text was measured using two texts from the reading test section of the Israeli Psychometric SAT (The Center for Psychometric Tests, 1994). Each text contained a short story (17 sentences, 257 words each), which appeared in its entirety on the computer screen. Reading time was measured by requiring a button press upon beginning to read and again upon conclusion.

When reading was completed, the text disappeared from the screen and six multiplechoice questions appeared one at a time. One of the two stories was read orally

and decoding errors were recorded to obtain a measure of accuracy. Comprehension scores were based on the total number of correct answers across the two texts. Reading time scores were determined on the basis of the mean reading time across both texts. *Phonology*: (The Phoneme Recognition Test for Words and Pseudo-words, Ben-Dror & Shani, 1996). This test included two sections, each containing 20 words. In the first section, the experimenter read each word and pronounced a syllable within the word. The subject had to produce the word obtained by omitting the specified syllable. In the second section, the experimenter read each word aloud and specified a phoneme located at the beginning, middle or end of the word. The subject had to produce the pseudo-word obtained by omitting the designated phoneme. Scores were based on the total number of accurate responses and test performance time of the two subtests. *Orthography*: Parsing Test (Breznitz, 1997). In this test, 50 rows of 4 words each were presented as a continuous line of print (i.e. no blank spaces). The subject was asked to draw lines to indicate where between-word spaces should be. Scores were based on performance accuracy and total test performance time.

In addition, working memory was assessed using the *Opposites* test (Shani & Ben-Dror, 1998b) in which a sequence of adjectives, each of which has an opposite (for instance, tall/ short; big/small; black/white) were presented in an order of increasing series length. The set of adjectives was read aloud by the examiner and the participant was required to respond with the opposite of each adjective in the series, in the order in which the adjectives were presented (e.g. the response to 'tall-big-black' would be 'short-small-white'). The examiner continued until the subject failed two consecutive adjective sequences within the same set. The test was not time-limited, and scores were based on the number of correct responses. *Working Memory-Completion* (Shani & Ben-Dror, 1998a). This test was comprised of sets of sentences in which the final word was missing. The number of sentences in each series ranged, in ascending order, from 2 to 5. The examiner read each sentence aloud, and the participant was required to complete the missing word in the sentence. At the end of a particular set of sentences, the subject was asked to recall the completing words in the order in which they appeared. Each set contained two series of sentences. The test was continued until the subject failed two consecutive series. The test was not time-limited, and scores were based on the number of correct responses. Word Fluency Test (Breznitz, 1996; designed on the basis of Lezak (1993)). Participants were requested to generate two lists of words each beginning with a given letter ('resh' (r), and 'shin' (s)) and then a list of groceries. One minute was allotted for each list. The score was the sum of the words recalled in the three tasks.

3. Procedures and methods (fMRI)

3.1. Behavioral tasks

3.1.1. Stimuli   The stimuli were Hebrew words presented (throughout the experiment) one at a time at the center of the display. Stimulus durations were set individually for each individual participant to correspond to his/her routine reading rate (slow) and to a correspondingly faster rate (fast) (e.g. 200 and 300 ms, respectively). The 'slow' rates corresponded to very comfortable stimulus duration rates, about up to 20% slower than the rates previously determined in the baseline (self paced) measurements of the reading acceleration task (Breznitz, 1987). The slow presentation rates for each individual were set to ensure a level of performance on the task of more than 90% correct in a pre-test, and without any loss in accuracy in the 'fast' presentation rate. This procedure resulted in three different stimulus duration rates per item in each of the tasks.

3.1.2. Tasks   There were three reading related tasks, each presented in two presentation rates.

Single words (SW). Subjects were required to make a semantic judgment (abstract/concrete) on Hebrew nouns of medium high frequency, each 3-6 letters long. The timing (stimulus duration) times were either 200, 300 or 550 ms for each word and a patterned mask (three superimposed 6 letter non-words) immediately followed for twice the target word presentation time. Each word was presented once with a stimulus onset asynchrony of 2 s, i.e. at a rate of 1 word (and corresponding mask) every 2 s.

Non-word (NW). Subjects were required to indicate (in a two alternative forced choice) whether each target pseudo-word contained two similarly sounding elements (phonological judgment). Each display item consisted of a single pronounceable non-word made of three distinct Hebrew phonemes. Half the target pseudo-words contained two identical phonemes but with non-identical orthography (a redundancy possible in Hebrew). Thus, the task required effective grapheme-to-phoneme translation for non-lexical words. The timing options were 400, 600, or 800 ms per target item durations and each target item was immediately followed by a patterned mask (three superimposed non-words of corresponding letter length) for twice the duration of the target item. Each pseudo-word was presented at a rate of 1 every 2.4 s.

Sentence reading (SNT). Subjects were required to make a plausibility judgment (in a two alternative forced choice) on simple sentences each made of four to six words presented one at a time. The timing options were 400, 550 or 650 ms per single word duration with a fixed between-words delay of 300 ms. The between sentence intervals were adjusted to maintain a mean rate of one sentence every 3 s.

A verb generation (VG) task was used as an independent means for defining language laterality as well as the extent of classical language areas (Broca's and Wernicke's

areas). In this task condition, the participants were required to silently generate a verb associated with the presented (target) nouns. Each target noun was presented for 800 ms without masking, however the targets were presented in one of two rates: 1 noun every 2 or 1 every 3 s.

3.1.3. Behavioral pre-test

Immediately before the imaging session each participant was given explicit instruction on the various tasks and then retested, in each task, to determine the individual setting of the stimulus presentation (target and mask duration) times during scanning.

3.2. MR brain imaging

A 2T-magnet system (Prestige, Elscint, Israel) equipped with echo-planar imaging capabilities was used. All studies were conducted at the MRI unit of the Division of Diagnostic Radiology at the C. Sheba Medical Center, Tel-Hashomer.

3.2.1. Scanning

During scanning subjects were supine in the magnet, with their heads immobilized by foam pads, and viewed the back-projected (computer controlled) stimuli through a mirror device. Responses were given using the dominant index finger. Tasks were administered in a pseudo-random order across subjects. Each task was presented in the two speed levels (fast and slow) and each task condition was repeated twice using a different word list for each repetition. Thus, the total number of experimental runs, per participant, were 14 (3 tasks $\times$ 2 timing conditions $\times$ 2 repetitions per condition (versions) +2 repetitions of the VG task).

3.2.2. Imaging parameters

T1 weighted, high-resolution, anatomical images were acquired for each participant, and used to determine the outline of regions of interest (ROIs) based on anatomical landmarks. For the functional brain imaging studies a gradient-echo EPI sequence (TR, 3000 ms; TE, 48 ms; flip angle, 90) was used to acquire 14×5 mm contiguous axial slices with the middle of the 4th slice aligned with the AC-PC line. In-slice resolution in the functional data was 3×2.67 mm (matrix size of 58×72). Thus, although the scanned brain volume included all structures from - 17.5 mm below, and extending dorsally to 52.5 mm above, the AC-PC plane, brain areas such as the dorsal aspect of the dorso-lateral prefrotal cortex, the dorsal parietal lobe and some ventral temporal lobe areas were not visualized.

3.2.3. Set (session) design

An alternating block design was used for all conditions and tasks with two task performance epochs (both of the same condition) alternating with three baseline epochs (fixation only). Forty-four time points (scans) were acquired in each set (baseline-taskbaseline-task-baseline, 12-8-8-8-8). There were 10

non-words (and masks) and 12 single words in each task interval (block) in the NW and SW conditions, respectively.

3.3. Data analysis Statistical analysis was performed using the general linear model as implemented in SPM99 (SPM99, Institute of Neurology, London).

3.3.1. Spatial pre-processing Due to scanner specific image distortions the standard MNI (Montreal Neurological Institute) SPM99 brain templates were not used as reference images. Instead a study specific template brain was generated from data from all participating subjects' brains using the SPM99-16 built-in software tools. In brief, the procedure included: creating a mean image for each subject (anatomical and EPI data); zero padding with a two-voxel layer in the coronal plane to avoid voxel losses; spatial co-registration using mutual information and re-slicing in 15 steps so as to telescope the data into the largest participant's brain; calculation of a new mean image and smoothing with a 10 mm Gaussian kernel.

For the anatomical template similar steps were involved: co-registration using mutual information of each anatomical scan to the non-smoothed version of the newly created EPI brain template; calculation of a mean anatomical image from the co-registered scans; normalization of the co-registered scans to this mean anatomical image; and creation of a new mean anatomical template from all the normalized anatomical scans. An additional segmentation and brain extraction stage followed by manual adjustments was performed in order to obtain an as optimal as possible three-dimensional model of the normalized brain space for data visualization.

The spatial normalization of the fMRI data sets required in most of the 16 cases the inclusion of a subject specific 'object masking' image file obtained by segmentation and brain extraction of the individual mean fMRI image (acquired during the realignment procedures) followed by a smoothing step (8 mm kernel size). Thereafter, subject specific normalization and non-linear regularization parameters were determined for each mean EPI image in respect to the EPI brain template with the use of the specific 'object masking image' file on an individual basis. The normalization of the regular EPI images was performed by applying those normalization parameters using the sinc-interpolation method followed by a last smoothing step with a large kernel size of 15 mm. Voxel size of all normalized data was $2 \times 2 \times 2$ mm.

3.3.2. SPM (statistical parametric mapping) analysis A comprehensive SPM model including 180 first-level effects: 3 tasks (SW, NW, SNT)×two presentation rates (slow, fast)×2 repetitions for each condition×16 subjects, was created. A box-car model, convoluted with the standard hemodynamic response function was used to contrast any given condition to its baseline as the first level analysis. To contrast between the two groups or between stimulus presentation rates within a task or between different

tasks, a second level analysis was performed based on a paired t-test. All significance levels reported were corrected for multiple comparisons across the whole available brain volume unless stated otherwise and were kept at $p < 0.05$. In the latter cases, a small volume correction (SVC) based on the Gaussian Random Field theory was applied defined by the following ROIs: left and right peri-sylvian language area, bilateral extra-striate visual areas, bilateral cunei and pre-cunei, and are shown in Fig. 1(a).

4. Results

4.1. Background behavioral measures   Analyses of variance (ANOVAs) were conducted in order to determine group differences between the dyslexic and normal readers on each of the baseline behavioral measures. The two groups were matched on non-verbal IQ (Raven standard progressive matrices) and no significant differences between the two groups were found in reading comprehension (Table 1). Significant differences were found between the two groups on most of the other baseline measures (Table 1). Dyslexic readers were both less accurate and slower than normal readers on measures of decoding, reading time, phonological, orthographic and working memory tests. Dyslexic readers achieved lower scores on the verbal fluency measures and were slower on the WAIS digit symbols and the symbol search.

4.2. fMRI measures   In all three tasks, there were no significant differences in terms of performance (accuracy) between the dyslexics and the normal readers. Moreover, there were no significant reductions in performance in the fast, as compared to the corresponding slow, stimulus presentation (duration) rate conditions in any of the dyslexic participants or normal readers; both groups maintaining above 90% correct performance. The imaging data analysis, on the other hand, showed some significant differential effects of the two stimulus duration rates on reading and script decoding in the two study groups, as well as clear differences in the pattern of brain activations induced by the various tasks in the two reading groups.

A summary of the main brain imaging results (significant differential activations) for the comparison of the two study groups is presented in Table 2(a-d). Data for the three reading tasks (SW, NW and SNT) for the two-stimulus presentation rate conditions (fast and slow) as well as pooled data across all three conditions and across both presentation rate conditions are shown. Both cluster size (number of activated voxels within a given area) and the t-score of the corresponding peak voxels are shown.

The largest differences between groups were found in the *NW* task in which participants were required to indicate whether each target pseudo-word contained or did not contain two similarly sounding elements (phonological judgment). Fig. 1(a) depicts the brain regions wherein significant activations (group average main effects) were evoked in the normal reading control participants, in the NW task. Both stimulus presentation

rate conditions (fast and slow) activated the left pre-motor and opercular areas, to a lesser extent the right frontal operculum, the left anterior insula, and bilaterally the intra-parietal sulci (including the left dorso-anterior supramarginal gyrus). Significant bilateral activation of the extra-striate cortices occurred in both presentation conditions, albeit stronger during the fast presentation, especially on the right. The anterior insula (including the internal frontal operculum) showed bilateral activation only for the slow presentation condition, with activation shifting to the right in the fast stimulus presentation condition.

Brain regions demonstrating a differential response during task performance in dyslexics and normal reading controls (voxel-based group analysis)

Region	Comp	Condition	Task	xyz	Size	t	p
(a) NW task							
L ant insula	d>c	slow		-32 36 -2	127	4.08	0.0002*
L front operculum	d>c	slow		-44 32 10	16	4.82	0.022 (SVC)
R pre-cuneus	d>c	fast		14 -50 38	68	4.97	0.0067 (SVC)
L ESVC	c>d	fast		-46 -48 2	7	4.48	0.0307 (SVC)
L ESVC	c>d	slow		-46 -50 -2	208	5.14	0.0065 (SVC)
(b) SW task							
L ESVC	c>d	fast	SW	-42 -52 8	118	4.68	0.0158 (SVC)
(c) SNT task							
R temp-parietal	c>d	fast	SNT	44 -54 0	28	4.55	0.0356 (SVC)
(d) Pooled data comparison (NW+SW+SNT)							
R pre-cuneus	d>c			14 -48 34	426	4.75	0.0008 (SVC)
L ant insula	d>c			-26 38 -6	53	4.31	0.0098 (SVC)
L premotor	d>c			-60 32 18	461	5.83	** (SVC)
R post insula	d>c			38 8 18	236	4.15	0.0007*
L ESVC	c>d			-48 -48 0	1806	9.63	*** (SVC
R ESVC	c>d			48 -38 -6	976	7.84	*** (SVC)
L Caudate	c>d						

Table. 2 Data for the two stimulus presentation rates (slow and fast) is shown: (a) SW task; (b) NW task; (c) SNT task; (d) data pooled across all three conditions (SW+NW+SNT). d>c, brain areas in which activity evoked by reading in the dyslexics significantly exceeds the activity level in the control subjects; c>d, brain areas in which activity evoked by reading in the control individuals significantly exceeded the activity level in the dyslexics. *, uncorrected significance levels were kept at $p < 0.001$; **$p < 10^{-4}$; ***$p < 10^{-9}$; SVC, small volume correction for multiple comparisons. L, left hemisphere; R, right hemisphere; ESVC, extra-striate visual cortex; ant., anterior; temp-parietal, temporo-parietal; IPS, intra-parital sulcus; MTG, middle temporal gyrus.
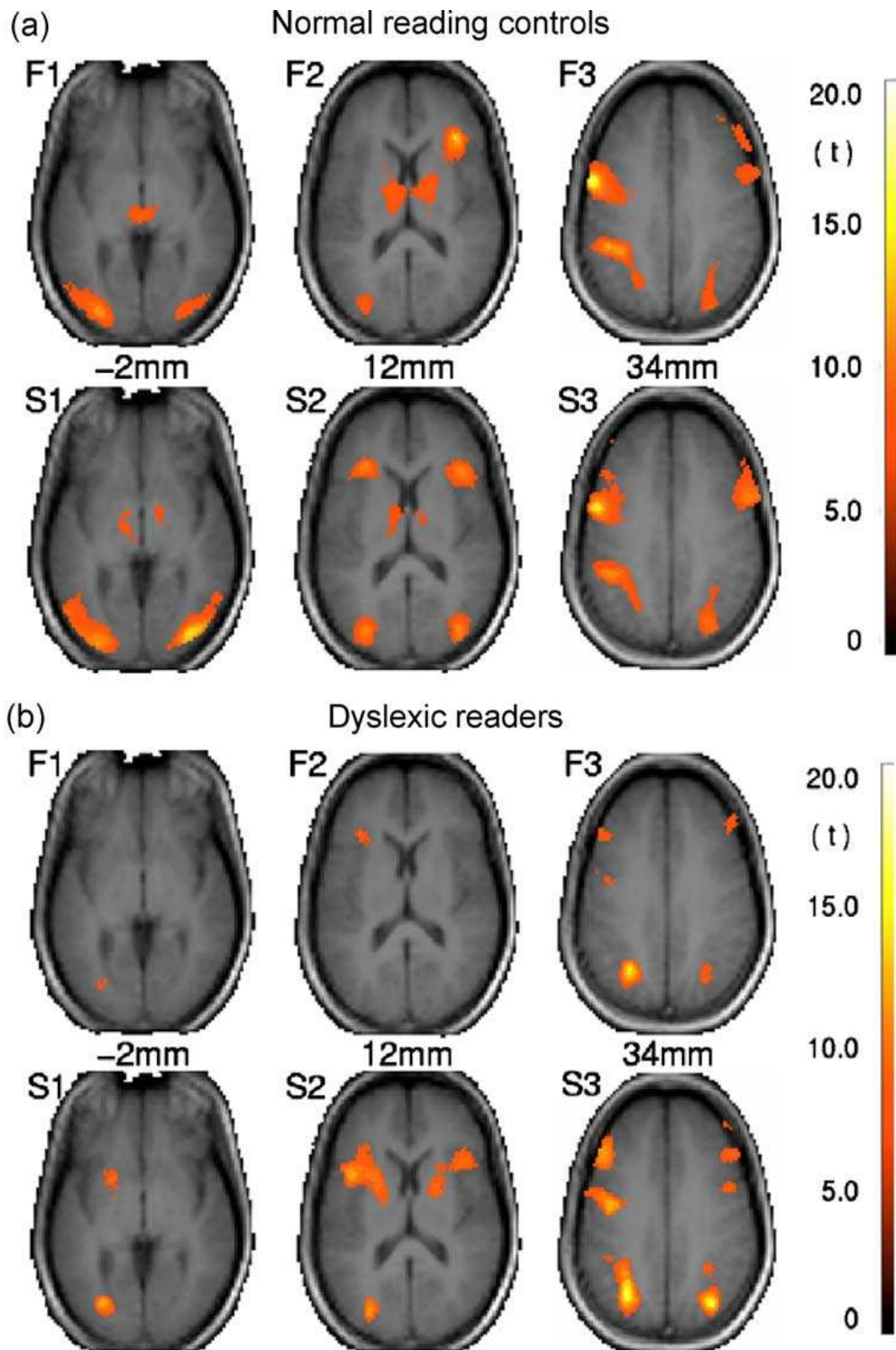
Fig. 1 Pattern of brain activations evoked in the NW task in the two reading groups: (a) normal reading controls; (b) dyslexic readers. Corresponding axial slices, oriented in the AC-PC plane are shown with their respective z coordinates (mm); $z = 0$ is the AC-PC line. F1, F2, F3-fast stimulus presentation rate ('fast' condition); S1, S2, S3-slow stimulus presentation rate ('slow' condition). There were clear activations in sub-cortical structures (the basal ganglia and thalami) as well but with no significant between group differences. The t-score threshold was at $p < 0.05$ corrected for multiple comparisons. The color bars represent the t-score range.

Fig. 1(b) depicts the group average main effects for the dyslexics in the fast and the slow presentation rates in the NW task. As in the normal reading controls the left pre-motor, the left anterior insula and bilaterally the intra-parietal sulci with some extension into the left dorso-anterior supramarginal gyrus were significantly activated in the slow condition, as well as the left extra-striate visual areas (no significant activation was found in the right extra-striate areas) and the left more than right dorso-lateral prefrontal cortex. In the fast condition, in addition to the parietal (regions related to the intra-parietal sulcus) activations (left more than right) significant activations were found in the left anterior insula and relatively less extensive activations in the dorso-lateral pre-frontal cortex and in the left extra-striate visual areas.
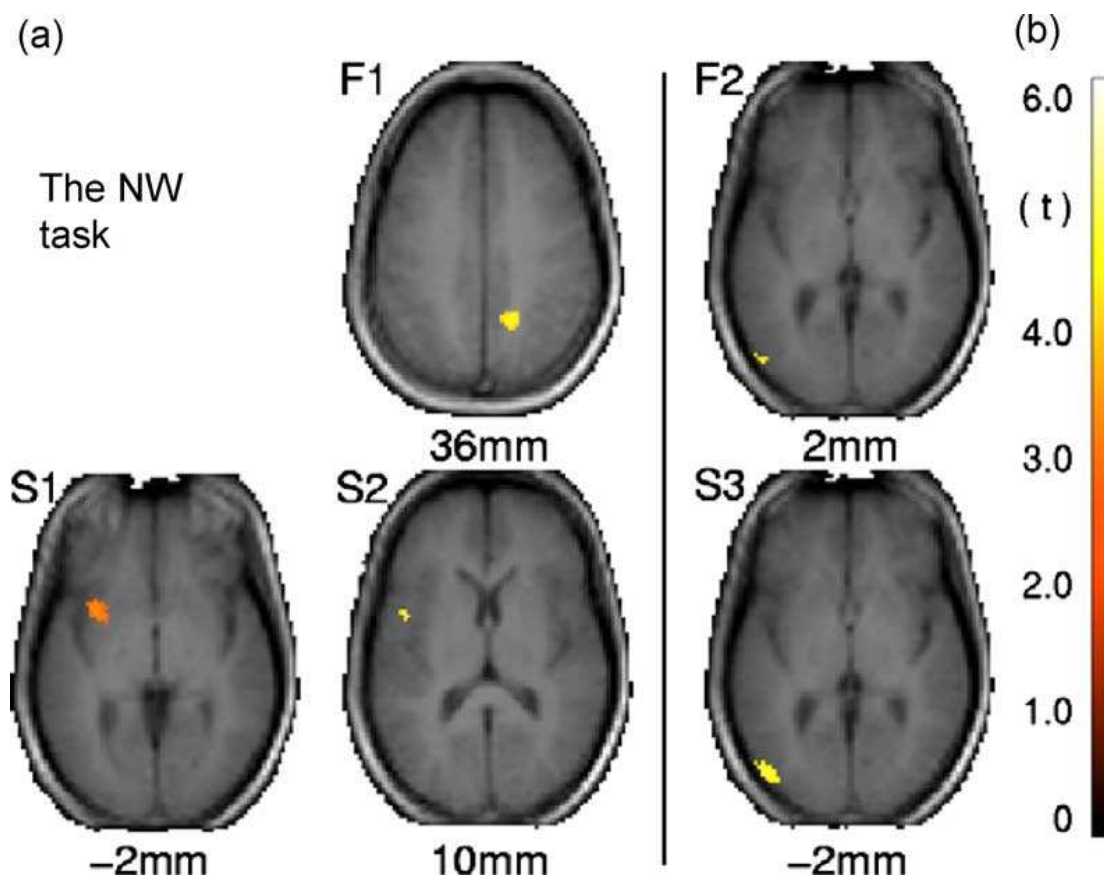
Fig. 2 Brain regions in which differential responses were evoked in the NW task in the two reading groups: (a) dyslexic>control readers; (b) control>dyslexic readers. F1, F2–fast stimulus presentation rate ('fast' condition); S1, S2, S3–slow stimulus presentation rate ('slow' condition). Axial slice level is indicated by the z (mm); $z = 0$ is the AC-PC line. The t-score threshold was at $p < 0.05$ corrected for multiple comparisons. The color bar represents the t-score range.

Fig. 2 and Table 2(a) present the main results of the comparisons between groups in the NW task. In the slow presentation rate condition, dyslexics, as compared to the normal readers, showed significantly higher activations in the left anterior peri-sylvian regions. The control readers, on the other hand, showed significantly more activation in the left (occipito-temporal) extra-striate cortex. However, the most surprising result (Table 1) was that the imposed acceleration of script decoding (the fast stimulus presentation condition) resulted in only minimal differences between the brain activation

patterns of the two reading proficiency groups (i.e. a relative 'normalization' of the evoked brain response patterns in the dyslexics' brains). The Rt pre-cuneus was the only brain area significantly showing stronger metabolic demands in the NW task in dyslexics *vs* control readers at the fast NW task and the differential activation in the left extra-striate visual areas was reduced. Analysis of the pooled data across both the fast and the slow NW conditions revealed that the main differences between the two population groups were somewhat similar to the differences found in the slow condition (Table 2(a)): in the dyslexics the left opercular regions, as well as the right pre-cuneus, were engaged significantly more (corrected, $p < 0.004$ and $p < 0.0006$, respectively) while the normal reading controls seemed to rely on their visual (extra-striate) areas (left more than right) (corrected, $p < 0.0003$ and $p < 0.0017$, respectively).

Brain response pattern in the SNT task ('slow' and 'fast' conditions) in normal reading controls

Region	slow			fast		
Region	xyz	t	p (corr)	xyz	t	p (corr)
L FO	-44 30 34	12.02	0.0005			
L premotor	-46 16 44	10.7	0.002	-46 14 44	9.26	0.013
L ant ins/IFG	-38 60 61	7.39	10-5	-46 62 4	4.27	0.0003
R ant ins	32 60 6	12.73	0.0003	42 60 4	10.81	0.0035
L MTG	-58 -14 -2	15.83	10-4	-48 -18 -6	11.11	0.0026
L ESVC	-30 -54 -6	9.53	0.0061	-26 -56 -6	8.7	0.022
R ESVC	34 -50 -6	9.69	0.0052	26 -58 -6	9.16	0.013

Table. 3   L, left; R, right; FO, frontal operculum; ant ins, anterior insula; IFG, inferior frontal gyrus; MTG, middle temporal gyrus; ESVC, extra-striate visual cortex. Corr., small volume correction.

The brain activation pattern in the SNT task in the normal reading control subjects is shown in Table 3. Significant activations were found for both presentation rate conditions in the left frontal operculum and bilaterally in the anterior insula as well as the left middle temporal gyrus. Bilateral small extra-striate activation foci were detected in the slow condition, and to a lesser extent in the fast condition. Significant activation was also found in the left pre-motor area.

In the normal reading controls, a comparison between the brain response pattern evoked by SW task as compared to the NW task revealed that a right posterior parietal cortex focus (24 -48 32) was more active in the NW task (corrected, $p < 0.005$). Only a very small difference in evoked response pattern was found when the SNT was compared to the SW task. This difference was in the left anterior middle temporal gyrus (-56 16 -6) (uncorrected, $p < 0.001$) which activated more in the SNT task.
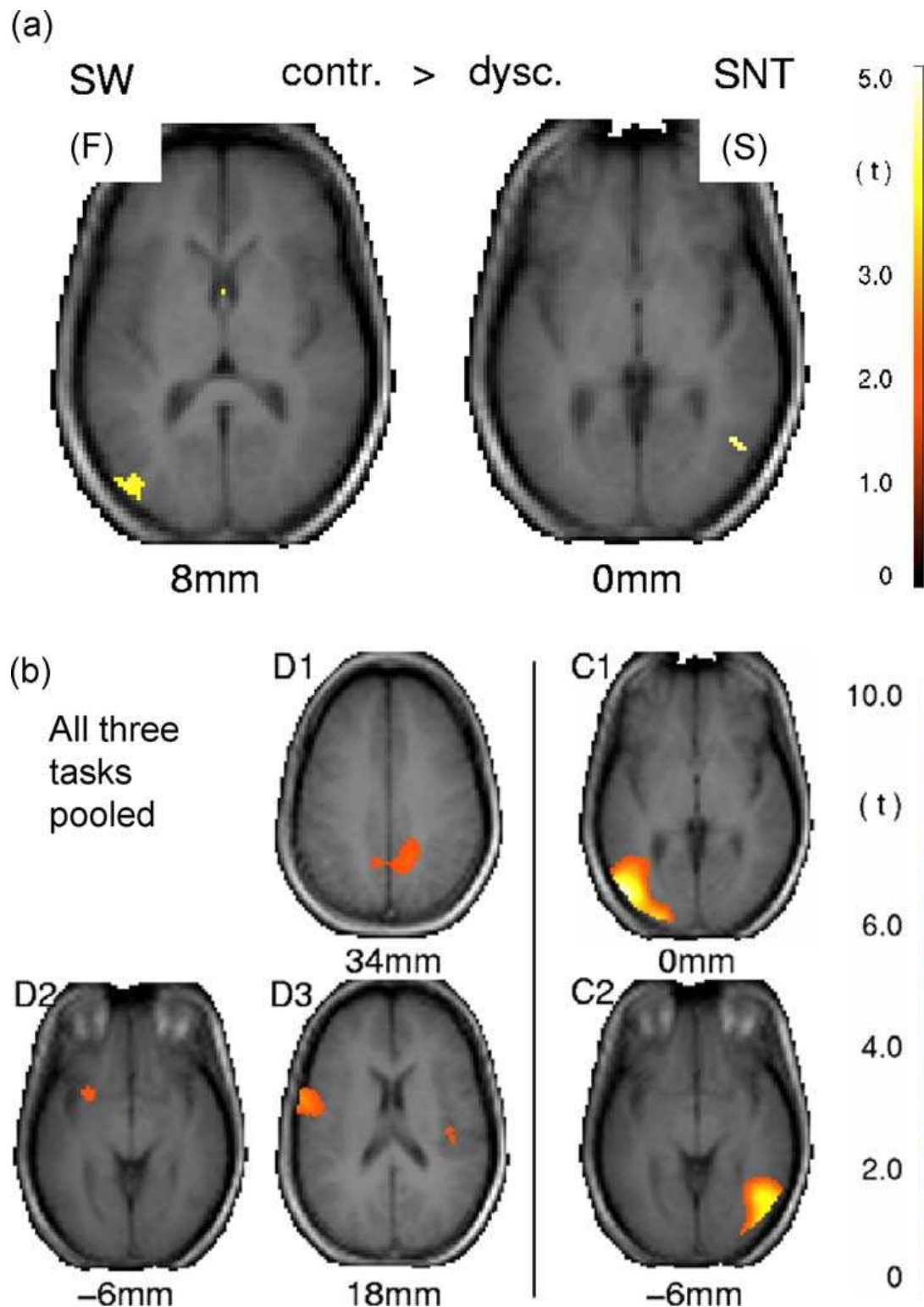
Fig. 3 Differential activations in dyslexic and normal reading controls. (a) Results for the SW (left panel) and the SNT (right panel) tasks. (F) fast stimulus presentation rate ('fast' condition); (S) slow stimulus presentation rate ('slow' condition). (b) Results for all three tasks pooled. D1, D2, D3 (left panels) depict brain regions showing more extensive engagement in the dyslexics' brains than in the normal reading controls. C1, C2 (right panels) depict brain regions wherein control readers had relatively higher brain activations compared to dyslexics. Axial slice level is indicated by the z (mm); $z = 0$ is the AC-PC line. The t-score threshold was at $p < 0.05$ corrected for multiple comparisons. The color bars represent the t-score range.

There were however, no significant differences in the evoked response patterns detected when the dyslexics, as a group, were compared to the normal reading controls, in

either the SW and the SNT tasks, in the slow condition (Table 2(b) and (c)). The only significant differences in the brain activation patterns of the two groups, were found in the fast reading conditions, with significantly more evoked activation in the left lateral extra-striate visual regions of the normal readers, compared to the dyslexics, in the SW task, and relatively increased activation in the posterior right temporal regions of the normal reading controls in the SNT task (Fig. 3(a)).

To enhance statistical power, the data from all three tasks was pooled (NW + SW + SNT) and the differences, between the two groups in the evoked brain activity across all three reading tasks, was compared in both the slow and the fast conditions (Fig. 3(b)). Due to the better statistical power (as compared to the analysis of each task by itself) the size of all activation clusters and their statistical significance were increased in the pooled data analysis. The results of the pooled data analysis (Table 2(d)) were consistent with the results of the analysis of the NW task. While the normal reading controls had significantly higher engagement (compared to the dyslexics) of the ventro-lateral extra-striate cortices (with a left hemisphere advantage), there were significantly higher activations, across all reading and script decoding tasks, in the left inferior frontal gyrus and the left parietal operculum as well as the Rt pre-cuneus. Thus, the pooled results indicate a larger reliance on left peri-sylvian regions in the dyslexics as compared to the normal reading controls.

5. Discussion

The current study was designed to explore the possibility that time-constrained reading (acceleration) may enhance reading effectiveness among dyslexic readers by prompting the dyslexic brain to process graphemic information in a manner different from the one engaged routinely (i.e. with no time constraints imposed) in reading. Altogether the results of this preliminary study of a small group of adult dyslexics suggest that for some reading tasks (semantic judgment of single words (SW) and sentence plausibility judgment (SNT)) increasing temporal constraints in script presentation may result in an uncovering of the differences between the brain responses evoked in adult dyslexics and normal reading adults but also in significant changes in the engagement of different brain regions in task performance. However, our results also show that in a non-lexical reading (script decoding) task (the NW task) the large differences in the evoked brain activity patterns in the two groups may have decreased with the increasing of the reading rate. This somewhat surprising finding is in line with the notion previously suggested in the context of the acceleration phenomenon. The fMRI BOLD imaging results thus clearly complement the previously reported findings from ERP studies wherein the effects of varying stimulus presentation rates were studied (Breznitz et al., 1993; Breznitz & Leiken, 2000; Leiken & Breznitz, 2001). These studies have shown that in both normal reading and dyslexic individuals ERP latencies (P200 and P300) appeared earlier in

the fast as compared to the slow stimulus presentation conditions. However, latency differences between the two presentation conditions were more pronounced in the dyslexic individuals, thus indicating that the dyslexics may come nearer to closing the gap, relative to normal reading control, in processing speed during the faster word presentation rates. Moreover, the spatial distribution (electrode) of the maxima of the ERP components were changed as a function of acceleration in both groups, suggesting that a qualitative shift in processing may also occur with accelerated stimulus presentation.

As a recent review (see Zeffiro and Eden (2000)) has pointed out, there has been continuous interest in the notion that neural systems, specifically those involved in phonological processing and phonological memory, can be strongly modulated by stimulus presentation and task performance rates. The demonstration that visual cortex activation was stimulus presentation rate dependent (Fox & Raichle, 1984) was extended in two landmark studies (Price et al., 1992, 1994) on listening to words and oral reading that showed that the engagement of frontal, temporal and parietal cortical areas, including those outside the primary and secondary sensory processing areas, may be stimulus duration dependent in quite a non-linear manner. Moreover, the stimulus presentation-duration dependent differences in brain areas engaged by task performance were not linearly related to performance (which was at ceiling). These findings may be related to the notion that time constraints on stimuli (visual or auditory) may cause a large differential response in dyslexics as compared to normal readers, because of a specific dysfunction in the magnocellular system (for review, see Zeffiro and Eden (2000)).

In the SW and SNT tasks, the only significant differences between the dyslexic readers and the normal reading controls (between groups comparison) in brain engaged in task performance were found in the fast condition with significantly more activation in the Lt extra-striate cortex of the normal readers, compared to the dyslexics, in the SW task and relatively increased engagement of the Rt temporo-parietal cortex in the SNT task. These findings are consistent with a number of studies (mainly of English) showing reliance on visual processing areas in phonological decision tasks (Paulesu et al., 1996; Pugh et al., 1996; Rumsey et al., 1997b; Shaywitz et al., 1998, in Zeffiro and Eden (2000)) and in reading (Bookheimer, Zeffiro, Blaxton, Gaillard, & Theodore, 1995; Price, Wise, & Frackowiak, 1996). In the rhyme detection task as well as in word recognition, Rumsey et al. (1992, 1997c) found that (along with other differences) the right inferior parietal regions exhibited regional cerebral blood flow increases in the normal readers compared to dyslexics. Moreover, it has been suggested that right parietal cortex engagement may decrease with increased experience in reading different scripts (Chee, Hon, Lee, & Soon, 2001). Novel word forms as in mirror reading (Poldrack, Desmond, Glover, & Gabrieli, 1998) and in reading a less well-experienced alphabet (Chen, Fu, Iversen, Smith, & Mathews, 2001) were also reported to correlate with higher right parietal activations. These activations decreased with increasing familiarity

with the novel scripts. Nevertheless, while the general trend for the differences between the two study populations is in line with results obtained in previous studies (with languages other than Hebrew) the comparison in the slow conditions failed to show any significant differences. One cannot rule out that this negative finding may be the result of insufficient statistical power (indeed the largest differences were found in the analysis of the pooled data). However, the finding of no difference between the two reading groups in the two reading tasks, SW and SNT wherein quite common lexical items were presented, may relate, in part, to the fact that the dyslexics were highly functioning adults who were all competent enough to study at university level. There are several studies showing that deficits in phonological processing are pervasive and persistent problems even in 'high functioning" adult dyslexics (Bruck, 1990, 1998). However, the most pronounced deficit in this group may be dysfluency (Levy, 2001; Meyer & Felton, 1999) i.e. the amount of text that can be read at a given time interval even by these high functioning individuals is very limited (Bruck, 1990, 1998; Brunswick, McCrory, Price, Frith, & Frith, 1999; Leong, 1999; Lovett et al., 1994).

The largest differences between the two reading groups were found in the *NW* task in which participants were required to indicate whether each target pseudo-word contained or did not contain two similarly sounding elements (phonological judgment). This task was unique in that for both participant groups, dyslexics and normal readers, the items presented were presumably novel and non-lexical to a similar degree. Thus, the effects of differential exposure (i.e. accumulating differential experience with lexical items) (Bitan & Karni, 2003; Ofen-Noy et al., 2003) were at minimum. In the slow presentation rate condition, dyslexics, as compared to the normal readers, showed significantly higher activations in the left inferior frontal regions (BA 44/6) including the frontal operculum. The control readers, on the other hand, showed significantly more activation in the left extra-striate cortex. However, the most surprising result—in line with our working hypothesis—was that the acceleration of reading (i.e. the same task performed at the fast rate) resulted in a relative normalization of the brain area engagement patterns in the dyslexic readers. It is reasonable to assume that at least in part this minimalization of the differences between the two reading groups was due to increased left frontal engagement in the normal readers group in the fast condition (Fig. 1(a)) in line with the results in the SNT task (Table 3). This interpretation is in line with the notion of presentation rate dependent shifts in activation patterns in normal reading individuals (Price et al., 1994) and also with the notion that in conditions wherein the reading tasks are more demanding (Chee et al., 2001; Clark & Wagner, 2003) the left inferior frontal cortex activation may increase. Nevertheless, the results from the rather phonologically demanding, and equally novel (to the two reading groups) NW task show that the differences between the evoked patterns of activation in dyslexics' and control reader's brains may decrease with timeconstrained script decoding, i.e. with the forced increase

of the reading rate. Moreover, the results of the first level analysis (Fig. 1) suggest that this normalization may also be due to a marked shift, in the dyslexics, in the relative engagement of different brain areas in task performance when stimulus presentation rates were increased.

Altogether, the results from the pooled data analysis (NW × SW × SNT) are consistent with the NW results in the slow condition. The results suggest that the dyslexics may rely more on the left peri-sylvian structures (i.e. canonical language areas) like Broca's area and the parietal operculum as well as the Rt pre-cuneus, while control readers made significantly more use of their extra-striate cortices (with a left hemisphere advantage).

The Hebrew dyslexics' left inferior frontal gyrus over-engagement in the NW task is in line with the findings in other languages (Paulesu et al., 1996; Shaywitz et al., 1997). There is a very large body of evidence linking the left inferior prefrontal cortex to phonological processes, and specifically this area's involvement in tasks requiring grapheme to phoneme translation (Chen et al., 2001; Clark & Wagner, 2003; Demonet et al., 1992; Fiebach, Friederici, Muller, & Von Cramon, 2002). There is also evidence that as reading becomes more proficient (and presumably more word form dependent) the involvement of left inferior frontal areas decreases (Clark & Wagner, 2003; Shaywitz et al., 1997). In a recent study, Chee et al. (2001) tested the effects of proficiency versus alphabeticality in Chinese-English bilinguals and found that reading in the less proficient language activated the left inferior prefrontal area as well as the bilateral parietal regions regardless of the specific language and irrespective of whether alphabetical decoding was possible. There is also some empirical support for the notion that the left inferior prefrontal cortex may be involved in the generation of rule-like behavior (Clark & Wagner, 2003; Tettamanti et al., 2002). Pooling the data of the fast and slow NW conditions showed that the main differences between the two population groups were as follows: dyslexics activated relatively more the left inferior frontal language area and the parietal operculum as well as the right pre-cuneus, while the normal reading controls seemed to rely on their visual (extra-striate) areas (left more than right). The extra-striate cortical areas have been implicated in proficient reading and phonological processing although these areas may also be related to orthographic processing (Clark & Wagner, 2003; Price et al., 1996; Rumsey et al., 1997a; Shaywitz et al., 1997).

Although the cuneus and pre-cuneus (bilaterally) were found to be over activated in previous studies comparing dyslexics to normal readers (Rumsey et al., 1997a), the current study design does not afford a clear explanation of the finding that the right pre-cuneus was the only brain area significantly showing stronger metabolic demand in the NW task in dyslexics *vs* control readers in the fast task condition. It is of interest that, using a task quite similar to the NW task, the cuneus and pre-cuneus were shown to be more active metabolically in a recent study comparing phonological

processing of English to 'Foreign' items (Clark & Wagner, 2003). The left lateral pre-motor areas showed significantly larger activation in the slow condition of the SNT and in the NW tasks in the normal readers (as well as in the dyslexics). As motor responses were made only during the stimulus presentation intervals (task performance epochs, blocks) the lateral pre-motor areas (the primary motor cortex hand area was not included in the scanned volume) may in part at least, be ascribed to the generation of motor responses. However, there are several indications that the lateral pre-motor areas, specifically the more ventral parts may be involved in various reading and phonological judgment tasks as well as verbal memory (Clark & Wagner, 2003; Paulesu et al., 1996; Rumsey et al., 1997b). The finding that these areas were specifically activated more in the slow condition in the SNT and NW task (given that the nature of the motor responses and their rates in the task activation epochs, were similar in all three tasks and stimulus presentation rate conditions) lends indirect support to the notion that this increased activation of left pre-motor areas was indeed task dependent. Thus, the relatively larger reliance on pre-motor areas in normal readers during slow sentence reading may indicate that the task demands were resolved through a stronger reliance on phonological processing, but less so in the time-constrained fast condition.

Hebrew has a shallow orthography and a characteristic (Semitic languages) morphology and may pose for the reader some unique problems compared to those encountered in English and related languages (Frost, 1994). The many points of similarity between the current findings and the large literature on English dyslexics support, however, the notion that the over reliance on Lt-IFG and the failure to evolve effective extra-striate processing routines may not be language specific. This proposal is in line with the notion of proficiency and familiarity with script systems as an important parameter in determining the pattern of brain activation in reading and script decoding (Bitan & Karni, 2003; Chee et al., 2001; Clark & Wagner, 2003; Price et al., 1996).

Altogether, our results show that: (a) no differences were found between the brain activation patterns evoked in the dyslexics and the normal reading controls in either the SW or the SNT task in the slow stimulus presentation condition. However, the normal reading controls had relatively larger evoked responses in (the mainly left) extra-striate visual areas when stimulus presentation times were shortened in the SW task. (b) The largest differences in the brain activation patterns, between the dyslexic readers and the normal reading controls, were evoked in the NW task. However, the differences between the two groups became smaller as the stimulus presentation durations were decreased, i.e. when reading and script decoding were performed with increasing time constraints (more differences in brain response patterns in the slow than in the fast conditions). (c) There were significantly higher activations, across all reading and script decoding tasks (pooled data), in the left inferior frontal gyrus (LIPC including Broca's area) and the left parietal operculum as well as the right pre-cuneus in the dyslexics. While the

normal reading controls had significantly higher activations (compared to the dyslexics) in extra-striate cortices (with a left hemisphere advantage).

Our results suggest that a manner of script processing much closer to the one employed by normal reading controls may be invoked, in well compensated adult dyslexics, given time constraints. Going somewhat beyond the data, these preliminary findings provide an indirect indication that the differences in processing scripts between dyslexics and normal reading adults may decrease with the increasing of the reading rate opening a way for a possible remedial approach—reading acceleration training for dyslexics. On a more general level our results raise the possibility, which can be empirically tested, that at least some of the reported differences in the patterns of brain responses ascribed to developmental, experiential factors and script system characteristics per se, and similarly at least part of the discrepancies between different study results may be related to different reading rates, and suggest that word presentation rates should be considered as important parameters in determining the manner in which otherwise similar tasks are processed in both dyslexic and normal readers.

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Effects of alphabeticality, practice and type of instruction on reading an artificial script: An fMRI study[*]

Abstract

In neuroimaging studies of word reading in natural scripts, the effect of alphabeticality is often confounded with the effect of practice. We used an artificial script to separately manipulate the effects of practice and alphabeticality following training with and without explicit letter instructions. Participants received multi-session training in reading nonsense words, written in an artificial script, wherein each phoneme was represented by 2 discrete symbols [7]. Three training conditions were compared: alphabetical whole words with letter decoding instruction (explicit); alphabetical whole-words (implicit) and non-alphabetical whole-words (arbitrary). Each participant was trained on the arbitrary condition and on one of the alphabetical conditions (explicit or implicit). fMRI scans were acquired after training during reading of trained words and relatively novel words in the alphabetical and arbitrary conditions. Our results showed greater activation in the explicit compared to the arbitrary conditions, but only for relatively-novel words, in the left posterior inferior frontal gyrus (IFG). In the implicit condition, the left posterior IFG was active in both trained and relatively novel words. These results indicate the involvement of the left posterior IFG in letter decoding, and suggest that reading of explicitly well-trained words did not rely on letter decoding, while in implicitly trained words letter decoding persisted into later stages. The superior parietal lobules showed reduced activation for items that received more practice, across all training conditions. Altogether, our results suggest that the alphabeticality of the word, the amount of practice and type of instructions have independent and interacting effects on brain activation during reading.

1. Introduction

Reading acquisition is associated with a change in the cognitive processes involved in reading. In most reading acquisition models, the evolution of skilled reading is related to the distinction between alphabetical and nonalphabetical reading, and the application of letter decoding knowledge [23,67,79,80,89]. While reading of alphabetical words may involve letter decoding (i.e., letter segmentation and grapheme-phoneme conversion), non-alphabetical words can only be read by the retrieval of word specific representations, consisting of either the whole word or based on salient features within the word. The dual route models consider these to be distinct mechanisms for reading [20-23], while connectionist models consider them as aspects of a single mechanism [47,70,79]. However, regardless of the question of whether letter decoding involves an abstract rule mechanism [20-23] or is a rule-like behavior based on the statistical regularities of the experienced script [47,70,79], most models of reading acquisition agree that the reliance on letter decoding changes in the course of training. Specifically, it has been suggested that in reading alphabetical words, the reliance on segmentation and letter decoding decreases with experience, and that reading familiar words becomes dependent on lexical non-alphabetical processes [23,80]*. On the basis of this assumption, neuroimaging studies that aimed to examine the difference between alphabetical and non-alphabetical reading often compared words and pseudo-words, or high and low frequency words [4,31,32,59,63]. The logic of these studies was that while high frequency words are expected to rely on direct retrieval of lexical representations, pseudo-words and low frequency words would rely on letter decoding since they have no effective lexical representation. One should note, however, that the design of natural script studies under this assumption confounds alphabetical reading with low amounts of practice and precludes the separate testing of each effect.

Neuroimaging studies that compared alphabetical and non-alphabetical reading in languages with two script systems (i.e., Japanese and Chinese) lead to conflicting conclusions, showing both similarities [58] and differences [59,77,78] between the script systems. Furthermore, even the comparison of Kana and Kanji (in Japanese) and of traditional Chinese characters with Pinyin (the alphabetical script) is confounded with morpho-semantic differences [17], as well as differences in word frequency and familiarity [41]. In addition, reading of traditional Chinese characters may not rely entirely on word-specific recognition processes due to the use of phonological cues in many of the characters. The aim of the current study is to use an artificial script in a functional imaging study to examine the separate effects of alphabeticality and the amount of experience and to test the hypothesis that the reliance on letter decoding decreases in the

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*Although different studies have shown greater involvement of phonological representations in word recognition in skilled reading [8,60,68], these studies did not differentiate between the level of the individual letters and the level of the word.

course of training on reading alphabetical words.

Another factor that may interact with the effects of alphabeticality and practice is the type of instruction given during training, and specifically whether explicit instruction on letter decoding is afforded [51]. There is an ongoing debate about the critical necessity of explicit instruction of phonological decoding rules for the acquisition of reading skills [35]. Previous reading acquisition studies have shown that explicit instruction on phonological decoding enhanced reading acquisition [3,5,14,36,37,40,66,80,91] and see [23] for review. Moreover, mere exposure to alphabetical orthography was, in many cases, insufficient for inducing the discovery of the alphabetic principle in children [12,13,15,29,53,87]. However, other studies suggest that training on whole word reading may elicit learning of grapheme- phoneme correspondences by young beginning readers [30,67,86,87,89] and may even be advantageous compared to explicit instruction of letter decoding [40].

In two recent studies [6,7], we directly addressed the question of whether whole word training results in the formation of letter representations and phonological decoding skills in literate adults. Participants received multi-session training in reading nonsense words, written in an artificial script, in which each phoneme was represented by 2 discrete symbols. Three training conditions were compared in terms of the time-course of learning and the ability to generalize the acquired knowledge (transfer): alphabetical whole words with letter decoding instruction (Explicit); alphabetical whole words without letter instruction (Implicit), and non-alphabetical whole words, with no consistent correspondence of letters to sounds (Arbitrary). Our results [6,7] showed that training in the explicit and arbitrary conditions resulted in distinctive learning processes. The pattern of transfer results suggested that training in the explicit condition resulted mainly in learning to recognize the individual letters, but also in some word-specific recognition. Training in the arbitrary condition resulted in word-specific recognition that was based on recognition of the internal structure of symbols in the word. Furthermore, performance in the explicit condition was more accurate, but slower than performance in the arbitrary condition, presumably because it involved letter decoding. Training in the implicit condition, resulted in word-specific recognition in all participants, in addition to non-declarative letter decoding knowledge in some participants. However, letter knowledge in the implicit condition was lower than in the explicit condition, and evolved only under specific facilitating conditions. The three training conditions did not differ only in terms of the type of knowledge that was acquired, but also in terms of preservation of learning gains. The acquired knowledge was better preserved in the explicit compared to the arbitrary and implicit conditions both between sessions, and in terms of long-term testing. This finding suggests that training in the explicit condition reached a higher, more progressed, level of skilled performance [7].

In the current study, we used the Morse-like artificial script, studied in Bitan and

Karni [7], to test the interaction between the effects of the alphabeticality and the amount of experience following training in either explicit letter instruction or whole word training conditions on brain activation during reading. The separate manipulation of alphabeticality and the amount of practice enabled the examination of the hypothesis that reading of familiar (well practiced) alphabetical words does not necessarily involve letter decoding. The use of an artificial script enabled us to control the amount of practice participants received on specific words (alphabetical and non-alphabetical) by comparing trained words to less trained words. Furthermore, the inclusion of arbitrary items afforded a condition wherein the script was devoid of any alphabetical or phonological cues, which is not the case in high frequency words in natural scripts. Finally, the use of non-sense words in a phonological "translation" task eliminated the effect of semantic processes, which is confounded in the comparison of words and pseudo-words.

Our results showed that alphabeticality, the amount of practice and the type of instruction, may each (independently) affect the patterns of brain activation evoked by reading. Our results suggest that explicit training on alphabetical words relied more on letter decoding in initial as compared to later stages of reading, with the reading of highly familiar, well-trained alphabetical words much less dependent on word segmentation and letter decoding. Nevertheless, explicitly well-trained alphabetical words elicited a different pattern of activation compared to the one elicited by non-alphabetical words in the arbitrary condition, even though both of them presumably resulted in reading that did not rely on letter decoding. The pattern of activation following the implicit training on alphabetical words suggests that the reliance on letter decoding persisted to later stages of training, as compared to the explicit condition.

2. Method

2.1. Subjects   16 right-handed female volunteers, ages 22-26, native Hebrew speakers with normal linguistic and reading skills participated in the experiment and were paid for their time. Each subject participated in two training conditions: an alphabetical condition and an arbitrary condition, serially.

2.2. Behavioral phase

2.2.1. Stimuli   The stimuli and the procedure of the behavioral phase were identical to those used in Bitan and Karni [7]. The training stimuli consisted of two sets of 12 nonsense words written in an artificial Morse-like script. Four consonants and two vowels were used to compose all non-words in a given set, with each element repeating six times in a set, e.g.:

Set 1: LOP, PNO, APL, TOL, TPO, NAL, NLO, LAT, ONT, PNA, APT, TNA.

Set 2: RUB, BMU, MUR, BRI, UMK, MIR, BKU, KRU, IRK, KMI, IMB, BKI.

We used a Morse-like artificial script in which a sequence of 2 symbols represented one letter, and 4 symbols, in different orders, were used to compose all letters. Each symbol appeared in 3 out of the 6 letters. (e.g., P: ＊ < L: < ＊ T: □ ⊨ A: ⊨ □ N: ＊ ⊨ O: < □). Two different transformations were used to represent the non-word in the novel script: an alphabetical transformation, in which each phoneme consistently corresponded to a letter (e.g.,: PNO: ＊ < ＊ ⊨< □ LOP: < ＊ < □＊ <), and an arbitrary transformation, in which phoneme to letter correspondence differed across words (e.g.,: PNO: □ ⊨⊨ □＊ < LOP: ＊ << ＊＊ ⊨). Thus, the symbol strings in the arbitrary condition could only be read as logographs (in similarity to Japanese Kanji).

For each set of training stimuli, four transfer tests were composed, 12 non-words in each test (Table 1). The word-transfer test consisted of new non-words composed of the original letters, and written with the same set of symbols (see examples in Table 1). The letter-transfer test consisted of new non-words composed of new letters written with the same set of symbols. A comparison of word transfer to letter-transfer served as the indication for the acquisition of letter decoding knowledge. A third transfer test was the symbol-transfer test in which the original non-words were written using a new set of symbols, with consistent mapping between the sets of symbols. Thus, the pattern of symbol repetitions and internal symmetries within each string was preserved. The fourth transfer test was the grapheme-transfer test, in which the original non-words were written using a still new set of symbols, in a completely new sequence. A difference between symbol-transfer and grapheme-transfer would indicate learning of the pattern of symmetries and repetitions in the sequence of symbols.

	Trained items ≈200 repetitions	Word transfer ≈30 repetitions	Symbol transfer ≈30 repetitions	Letter transfer	Grapheme transfer
Explicit N=8	PNO: ＊<＊⊣<□ LOP: <＊<□＊<	NOP: ＊⊣<□＊< POL: ＊<<□<＊	PNO: -ㅠ- ^ㅠ(LOP: ㅠ-ㅠ(-ㅠ	DUF: ⊣＊<⊣□< SFU: □⊣□<<⊣	PNO: ⊦]◊]⊦∩ LOP:]◊⊦∩⊦]
Implicit N=8	PNO: ＊<＊⊣<□ LOP: <＊<□＊<	NOP: ＊⊣<□＊< POL: ＊<<□<＊	PNO: -ㅠ- ^ㅠ(LOP: ㅠ-ㅠ(-ㅠ	DUF: ⊣＊<⊣□< SFU: □⊣□<<⊣	PNO: ⊦]◊]⊦∩ LOP:]◊⊦∩⊦]
Arbitrary N=16	PNO: □⊣⊣□＊< LOP: ＊<<＊＊⊣	NOP: ＊<＊⊣<□ POL: ＊<□⊣⊣□	PNO: -ㅠㅠ-(^ LOP: (^^ ((ㅠ	DUF: □<⊣＊<⊣ SFU: □<□⊣<⊣	PNO: ◊]⊦]⊦∩ LOP: ⊦∩]◊⊦]

Table 1 Summary of conditions presented at the behavioral phase. Conditions administered during scanning are displayed in bold lines, with the amount of experience afforded prior to scanning indicated in terms of the number of repetitions per item. Two out of a total of 12 items are presented as an example in each condition. For convenience of comparison, all examples are presented from a single set of stimuli. In practice, a different set was used in the alphabetical and in the arbitrary condition in each subject.

2.2.2. Apparatus The stimuli were presented on a 17-in. 60 Hz. PC screen, with each item subtending 1- viewing angle, from a viewing distance of 60 cm. Stimulus presentation as well as the recording of responses (using a standard three button mouse), was controlled by 'Psy', a psychophysical measurements program, operating on Linux environment (Bonneh, 1998).

2.2.3. Experimental procedure   Each subject was trained in two training conditions successively: an alphabetical condition—training on alphabetical non-words, and an arbitrary condition—training on non-alphabetical non-words with no consistent mapping of graphemes to phonemes. In the alphabetical condition, half of the subjects were trained in the 'explicit' condition—given instruction on the grapheme–phoneme correspondence prior to training, and half of the subjects were trained in the 'implicit' condition—with no instruction of grapheme–phoneme correspondence. In each group, half of the subjects were trained on the arbitrary condition before the alphabetical condition, and half of the subjects were trained on the alphabetical condition before the arbitrary condition. The two sets of trained non-words were written using a different set of symbols and were balanced across training conditions.

Fig. 1 shows that the first session of each training condition started with a 'whole-word instruction' block, in which the subject was presented with each target non-word in novel script with its corresponding translation to Latin letters below. Each stimulus was presented for 2000 ms and subjects were instructed to read it aloud and memorize the association. A 'letter-instruction' block was given prior to the 'whole-word instruction' block only in the explicit training condition. The 'letter-instruction' block consisted of 30 trials in which the individual letter patterns in the new script were presented together with their corresponding Latin letter translation, each pair for 2000 ms. Subjects were required to pronounce the related phoneme and memorize the association. The letters appeared in a fixed order that repeated for 5 times (total of 30 trials).

After the instruction block(s) 6 training blocks was administered. In each trial, a target word appeared for 800 ms with a Latin-letter-string presented below. Half of the trials in each block contained correct pairs, and half of the trials were incorrect pairs. The subject's task was to indicate, for each test item, whether the Latin-letter-string was the correct translation, by pressing one of two keys (two alternative forced choice). Auditory feedback was given for errors. Each block consisted of 48 trials. In each training condition, subjects were given training on 5 daily sessions, spaced 1-3 days apart. In sessions 2-5, only the training blocks were administered, and the training procedure was identical in all conditions.

At the end of the 5 training sessions, the transfer of learning gains to novel stimuli was tested (Fig. 1). Each of the four transfer tests was administered in a separate session with the order of transfer tests fixed for all subjects (i.e., word-transfer, symbol-transfer, letter-transfer and grapheme-transfer). In each of the 4 transfer session subjects first performed 3 blocks of the task using the originally trained non-words. The level of performance of the task with the trained stimuli served as the reference for calculating the transfer of performance gains to the transfer stimuli. Subjects then performed a 'whole-word instruction' block in which the transfer stimuli and their Latin letter equivalents were presented. No 'letter-instruction' was given during the transfer sessions. Finally,

subjects performed 6 blocks of the task using the transfer stimuli. A transfer ratio was calculated for each subject in each transfer condition in the following manner. The difference between the mean performance in the transfer blocks and mean performance in the first training session was divided by the difference between the last performance of the original stimuli (in the transfer session) and performance in the first training session.

$$\text{Transfer ratio} = \frac{(\text{Transfer - Trained 1st session})}{(\text{Trained last session - Trained 1st session})}$$

All data were analyzed using the General Linear Model (GLM). 1 outlier of more than 2 standard deviations from the mean was excluded from the analysis of the behavioral results in the explicit-letter-transfer, and explicit-grapheme-transfer conditions. This subject was included in the analysis of the fMRI results since these conditions were not performed during scanning.
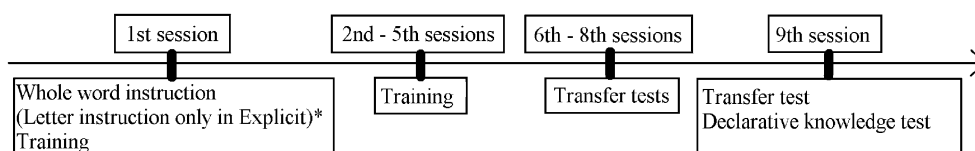
Fig. 1 Design of the behavioral phase. (*) Letter instruction was given only in the 1st session of the explicit training condition.

2.3. fMRI phase

2.3.1. Stimuli Non-words from six of the conditions presented in the behavioral phase were examined during scanning: alphabetical trained words, alphabetical word-transfer, alphabetical symbol-transfer, arbitrary trained words, arbitrary word-transfer and arbitrary symbol-transfer (see Table 1). 12 items in each of the six conditions were presented twice, making a total of 144 trials per subject. Prior to scanning each trained item has been repeated for 230 times, and each transfer-test item has been repeated for only 30 times. Hence, the difference between trained and transfer items represents the changes that depend on the amount of practice.

2.3.2. Experimental procedure The event-related fMRI scans were acquired on average 20 weeks after training. A previous study [7] showed that learning gains were preserved even 13 months after training. However, to ensure participants' high level of accuracy during scanning two refreshing sessions were performed during the preceding week. In the first refreshing session, participants performed 6 blocks of training in each training condition (i.e., alphabetical and arbitrary), and 2 blocks of each transfer condition (i.e., alphabetical word-transfer, alphabetical symbol-transfer, arbitrary word-transfer, and arbitrary symbol-transfer). In the second refreshing session, participants performed 4 practice blocks in which all 6 conditions were mixed in a pseudo-random

order, with presentation procedure and duration matched to the presentation in the scanner (see below).

In the scanner, 144 trials were presented in four sets of 36 trials each. In each set, half of the items (six) from each of the six conditions were presented in a mixed pseudorandomized order. Each trial began with a 400-ms fixation circle, followed after 300 ms by the target word presented for 2000 ms. The Latin letters string was presented 6800 ms after the target word for 400 ms, followed by an interval of 6100 ms before the beginning of the subsequent trial. Altogether, each trial lasted 16 s (Fig. 2). In similarity to the behavioral phase, subjects were required to judge whether the translation was correct and indicate their decision by a hand movement to one of two directions. Trials with incorrect responses were excluded from the analysis. In addition to the experimental task, a verb-generation task was administered in 2 sets of scans to determine the subjects' hemispheric dominance.
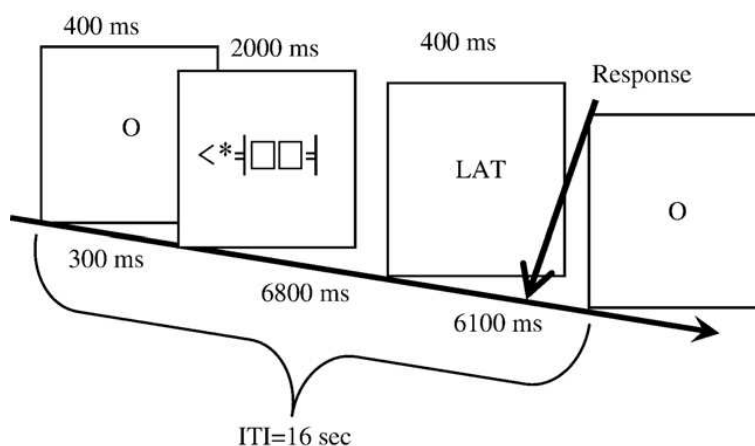
Fig. 2 The temporal sequence of displays in a single trial (16 s) during scanning.

2.3.3. Data acquisition and analysis fMRI scans were acquired in a 3T GE Signa scanner, equipped with a birdcage head coil. Subjects' heads were immobilized using foam pads. Visual stimuli were back-projected by an RF-shielded projector system and viewed through a mirror device. The functional data were acquired using gradient echo planar imaging (GEPI) sequence, with TR = 3 s, TE = 35 ms and flip angle = 90°. 24 slices, 5 mm thick, were acquired parallel to the AC-PC plane, and covered the whole brain. Field of view (FOV) was 24×24 cm, and in plane resolution was 3.75×3.75 mm. For each subject, 4 MRI sessions of 196 volumes were acquired, while the first 4 volumes were discarded to allow for T1 equilibrium effects. T1-weighted anatomical images were obtained with TR = 400 ms, TE = 14 ms, flip angle = 80°, resulting in a data matrix of 256×256 voxels of 0.94×0.94 mm.

Data were analyzed with the Statistical Parametric Mapping software (SPM2, Wellcome Department of Imaging Neuroscience, London). The images were synchronized to the middle slice to correct for differences in slice acquisition time, spatially realigned to the first volume to correct for head movements, and normalized to the standard EPI

template volume (MNI). The data were then smoothed with a Gaussian kernel of 10 mm.

At a first stage, data were analyzed individually for each subject and condition. Conditions were convoluted with the canonical hemodynamic response function (HRF) and highpass filtered with a cutoff period of 128 s. Each of the six conditions, and each of the two stimuli presented in a trial (i.e., artificial script and Latin letters string) modeled separately. The t-value contrasts, for each condition contrasted against the overall mean from the individual subjects were ultimately imported into a second level analysis (random effect). In order to contrast the various group effects, the following tests and comparisons were applied: (1) Group main effect for each condition was tested using the onesample t-test. (2) The effect of alphabeticality (alphabetical vs non-alphabetical) for each condition (i.e., trained words, word-transfer and symbol-transfer), and the effect of practice (i.e., trained vs transfer conditions) were tested using a paired t-test. (3) The differences between the explicit and implicit conditions were tested by using a two-sample t-test.

In addition, the correlation between brain activation and the accuracy of performance in the behavioral phase was tested. A 'multiple regression with constant' analysis was performed, with the individual's mean accuracy in the transfer session (or in the 9th session for trained items) serving as the covariate. The performance during scanning was not used as a covariate since it was at ceiling level and had less variance. Moreover, the performance during the training and transfer test may better represent the individuals' learning ability. Finally, the correlation of activation with the behavioral index for letter knowledge (word-transfer minus letter-transfer) was tested for alphabetical trained and word-transfer items.

Our focus of interest was primarily on the classical language and reading areas, i.e., left inferior frontal gyrus (BA 44/45) and the left inferior parietal lobule (BA 40). Hence, a small volume correction (SVC) was applied to the P values of activated voxels in these anatomically predefined ROIs. Other regions of activation are interpreted if they survived a threshold of whole-brain corrected P < 0.05. The figures and tables present clusters larger than 15 voxels at a threshold of uncorrected $P < 0.001$, for descriptive purposes. Correlation with behavior is reported with a threshold of uncorrected $P < 0.001$ within our regions of interest, and whole-brain corrected $P < 0.05$ outside our region of interest. Results are reported based on the WFU atlas [61,62].

Two subjects were excluded from the analysis due to hardware malfunction during scanning. An additional subject was excluded due to right-hemispheric activation patterns as observed in the verb generation task. This results in 6 subjects for the 'explicit' group and 7 subjects for the 'implicit' group. The behavioral results are shown only for subjects included in the fMRI analysis.
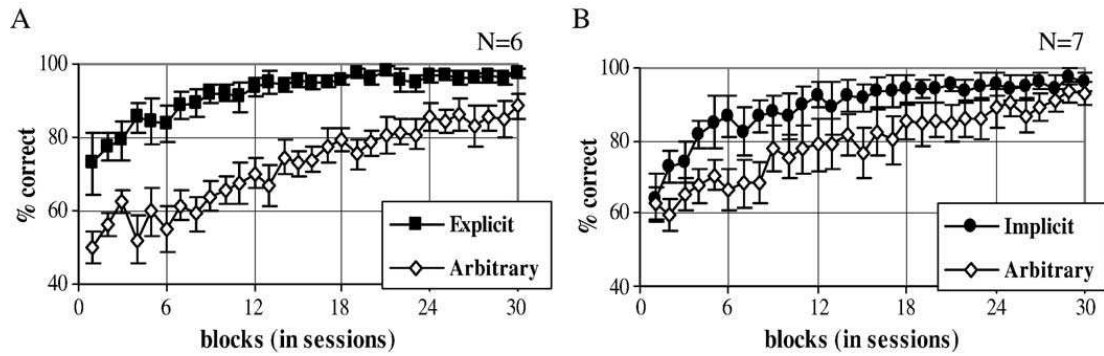
Fig. 3 Learning curves for the explicit group (A) and the implicit group (B). Accuracy of performance is shown for the alphabetic and the arbitrary conditions. Vertical lines indicate final blocks of each training session.

3. Results

3.1. Behavioral   All training conditions induced significant improvement in the translation task, both in terms of accuracy and in terms of reaction time (RT), with no speed-accuracy tradeoffs. The GLM analyses with group and condition order as between-subject variables, and training-condition, session and block as within subject variables, showed significant effect of session ($F(4,40) = 135.9$ and $F(4,40) = 49.5, P < 0.001$, for accuracy and RT, respectively) and block ($F(5,50) = 30.1$ and $F(5,50) = 27.1, P < 0.001$ for accuracy and RT, respectively). However the time-course of learning was different in the different training conditions. Figs. 3A, B show that the performance in both alphabetical conditions was more accurate compared to the performance in the arbitrary condition throughout the entire training process. A GLM analysis of the two groups revealed a significant difference between alphabetical and arbitrary conditions ($F(1,10) = 32.7, P < 0.001$). Within group analyses revealed a significant difference between the explicit and arbitrary conditions ($F(1,4) = 193.1, P < 0.001$) (Fig. 3A), and a non-significant trend for higher accuracy in the implicit compared to the arbitrary condition ($F(1,5) = 6.0, P = 0.06$) (Fig. 3B).
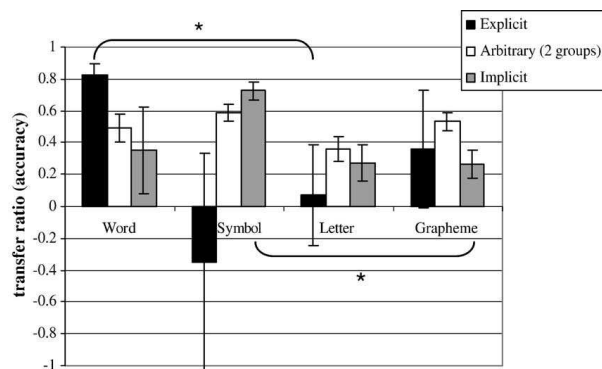

Fig. 4 Transfer results in the Explicit (one group), Implicit (one group) and Arbitrary (two groups) conditions. The measure for transfer was calculated as: (mean performance in the transfer session À first training session)/(last training session À first training session), with transfer ratio of 1.0 indicating full transfer. (*) Significant difference $P < 0.05$.

Between group analysis of the accuracy showed no significant difference between the explicit and implicit conditions ($F(1, 10) < 1$). However, analysis of RTs showed significantly faster responses in the implicit compared to the explicit condition throughout training ($F(1, 10) = 17.9, P < 0.01$).

The results of the transfer tests indicate that the ability to transfer the acquired knowledge to untrained stimuli was markedly different following training in the explicit and arbitrary conditions (Fig. 4). Performance in the word-transfer test in the explicit condition was significantly higher than performance in the letter-transfer test ($t(4) = 2.8, P < 0.05$)) (Fig. 4). The advantage of words composed of the original letters compared to words composed of new letters suggests that the letter knowledge was acquired in the explicit conditions. Nevertheless, accuracy of performance in explicit-word-transfer items, was lower than in trained items (word-transfer ratio < 1). Although the significance of this difference may not be tested statistically, it may suggest that participants in the explicit condition have acquired some word-specific knowledge in addition to the letterknowledge. As expected, there was no advantage of word-transfer over letter-transfer in the arbitrary condition $t(5) < 1$. Moreover, in the explicit group, performance in the word-transfer test was significantly higher in the explicit condition than in the corresponding arbitrary condition ($t(5) = 2.5, P < 0.05$) (Fig. 4).
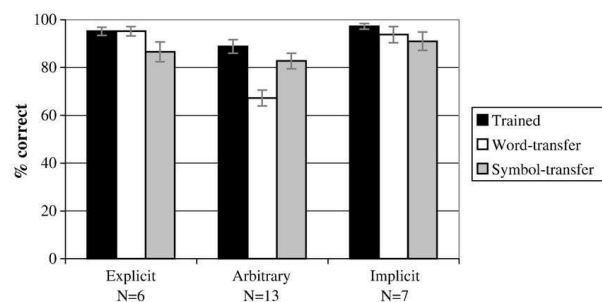
Fig. 5 Accuracy of performance during scanning, mean percent correct and standard errors are shown.

Participants' mean accuracy of performance within the scanner was 0.86 across all conditions (Fig. 5). A GLM analysis, with training condition (alphabetical *vs* arbitrary) and test-type (trained, word-transfer, symbol-transfer) as within subject variables, and group (explicit *vs* implicit) as a between subject variable was conducted on the accuracy of performance in the scanner. A significant main effect was found for the training condition ($F(1, 11) = 36.0 P < 0.01$) and test-type ($F(2, 10) = 14.8, P < 0.01$) and a significant interaction between training condition and test-type ($F(2, 10) = 11.2, P < 0.01$). Paired *t*-tests found that the arbitrary-word-transfer condition a significantly lower accuracy compared to the alphabetical-word-transfer in both the explicit group ($t(5) = 8.3 P < 0.01$) and implicit group ($t(6) = 3.4, P < 0.05$). Accuracy in the arbitrary-word-transfer condition was significantly lower compared to the arbitrary-

trained condition in both the explicit group ($t(5) = 3.7 P < 0.05$) and the implicit group ($t(6) = 3.9, P < 0.01$).
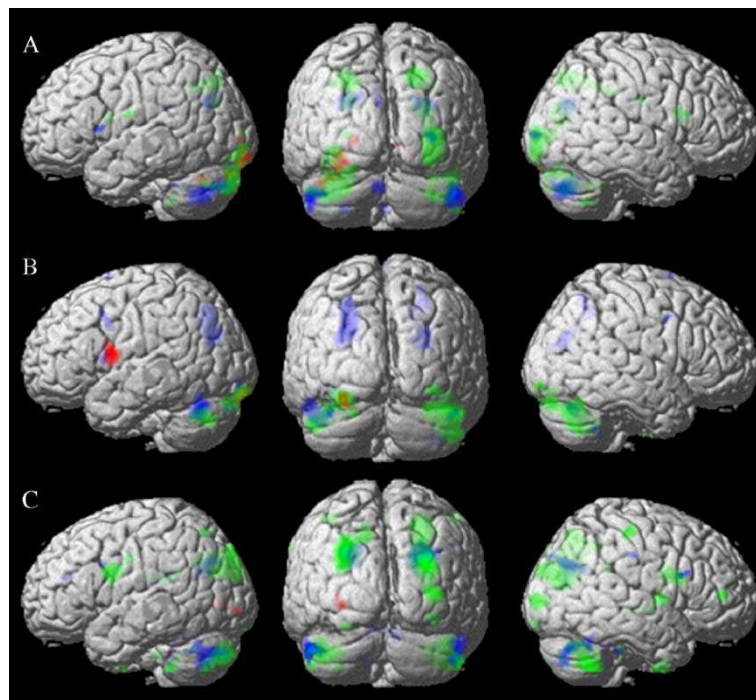
Fig. 6 Brain regions showing activation in the Explicit (red) Arbitrary (green) and Implicit (blue) conditions, in trained words (A), word-transfer (B) and symbol-transfer (C) items.

Fig. 4 shows that both the arbitrary and the implicit conditions resulted in a highest degree of transfer in the symbol-transfer test compared to the word and letter transfer tests (non-significant trend). In contrast to the explicit condition, following training in the implicit condition, there was no significant difference between word-transfer and letter-transfer (transfer ratios were 0.35 and 0.27, respectively, $t(6) < 1$).

3.2. fMRI

3.2.1. Comparison of the explicit and arbitrary conditions Fig. 6 and Table 2 show the patterns of activation evoked by reading in each of the single conditions. Reading of trained words in the explicit condition activated bilaterally the occipital cortex, with a larger cluster on the left including the calcarine and extending into the inferior occipital gyrus. Reading of trained words in the arbitrary condition activated much broader areas, again bilaterally, in the occipital cortices (including the inferior and middle occipital gyri), in parietal regions (the banks of the intraparietal sulci, inferior and superior parietal lobules), in the precentral gyri and in the insula. No clusters of activation exceeded the 15 voxels threshold in the direct comparison of explicit-trained and arbitrary-trained items (Table 3).

Regions of activation in individual conditions compared to the overall mean

Condition	Region	Brodman Area	Hemisphere	z score	Voxels	x	y	z
Explicit trained								
	Inferior occipital gyrus/cuneus	17/18	L	4.54	215	-36	-96	-18
	Lingual gyrus	18	R	3.61	41	14	-72	-4
Explicit word-transfer								
	Inferior occipital gyrus/fusiform gyri	18/19	L	4.06	68	-26	-94	-22
	Inferior frontal gyrus/insula	44/13	L	4.02	325	-46	0	12
Explicit symbol-transfer								
	Middle occipital gyrus	19/19	L	4.22	53	-32	-76	2
Arbitrary trained								
Occipital:	Inferior occipital gyrus/cerebellum	18	L	4.07	1043	-36	-94	-8
	Middle occipital gyrus	18	L	3.38	28	-26	-96	6
	Inferior occipital/middle occipital gyri	18/19	R	4.43	994	32	-98	-8
Parietal:	**Precuneus/inferior parietal lobule**	7/40	L	4.48	703	-22	-70	40
	Superior parietal lobule/precuneus/ supramarginal gyrus	7/40	R	4.32	843	22	-68	48
	Postcentral gyrus	43	L	3.88	49	-64	-10	20
Frontal:	Insula	13	L	3.84	98	-40	4	16
	Insula/inferior frontal gyrus	13/44	R	3.83	257	42	16	20
	Precentral gyrus	3	R	3.58	41	52	-16	30
	Medial frontal gyrus	6	L	3.59	15	-8	14	48
Arbitrary word-transfer								
	Inferior occipital/fusiform gyri/cerebellum	17/18	L	4.03	472	-26	-98	-18
	Inferior occipital/fusiform gyri	18	R	3.62	173	34	-94	-10
	Fusiform gyrus	37	R	3.59	18	48	-62	-24
Arbitrary symbol-transfer								
Occipital:	Fusiform gyrus	20	R	3.33	20	42	-30	-32
	Inferior occipital gyrus	17	L	3.43	24	-24	-98	-20
	Inferior occipital gyrus	18	R	3.56	46	36	-96	-18
	Middle occipital gyrus	19	R	3.96	199	34	-96	4
	Precuneus/superior occipital gyrus	7/19	L	4.10	1267	-20	-70	34
Parietal:	Cuneus/superior parietal gyrus	19/7	R	4.78	1842	30	-74	20
	Inferior parietal lobule	40	R	3.49	48	36	-42	28
	Superior parietal lobule	7	L	3.56	46	-40	-66	58
	Postcentral gyrus	3	R	3.69	145	48	-26	56
Frontal:	Precentral gyrus	6	L	3.36	25	-64	-10	36
	Precentral gyrus/basal ganglia	6	R	4.27	258	54	-2	6
	Insula	13	L	4.03	298	-34	-42	20
	Inferior frontal gyrus	9/44	L	4.77	429	-46	2	24
	Inferior frontal gyrus	46	R	4.05	59	54	46	8
	Inferior frontal gyrus	9/44	R	3.69	331	52	4	26
	Medial frontal gyrus	6	R	3.36	29	4	-28	60
Implicit trained								
Occipital:	Middle occipital gyrus	19	R	4.08	50	32	-96	4
	Precuneus	7	L	5.75	235	-18	-68	30
	Cuneus/precuneus	7	L	4.22	70	-4	-76	30
	Precuneus	7	R	4.46	238	26	-70	28
Frontal:	**Precentral/inferior frontal gyrus**	44	L	3.97	50	-54	14	8
Implicit word-transfer								
Occipital:	Inferior occipital gyrus	19	L	3.35	35	-46	-90	-12
	Cuneus/precuneus/superior occipital gyrus	7/19	L	4.55	646	-28	-72	24
Parietal:	Cuneus/superior parietal gyrus	19/7	R	3.65	399	28	-72	28
Frontal:	Precentral gyrus	44	L	3.43	26	-58	10	8
	Precentral gyrus	6/9	R	3.33	18	58	4	40
	Inferior frontal/middle frontal gyri	44/8	L	3.61	71	-46	6	36
Implicit symbol-transfer								
Occipital:	Precuneus	7	L	4.30	367	-22	-66	24
	Cuneus/precuneus	19	R	4.98	440	24	-70	28
Frontal:	Precentral gyrus	6	R	4.09	33	50	-22	38
	Middel frtonal gyrus	46	L	3.57	16	-40	38	20
	Inferior frontal gyrus	45	R	3.84	43	56	18	24
	Inferior frontal gyrus	9	L	3.34	20	-48	10	32

Table. 2 Clusters larger than 15 voxels are presented at a threshold of uncorrected $P < 0.001$. Clusters significant at a threshold of small volume corrected $P < 0.05$ are indicated in bold.

Reading of word-transfer items in the explicit condition showed robust activation in the posterior left inferior frontal gyrus (LIFG) including the pars opercularis of the left inferior frontal gyrus (BA 44). This cluster survived small volume correction for the anatomically predefined ROI (Table 2). Reading of explicit-word-transfer items also activated the left occipital cortex (inferior-occipital/posterior-fusiform gyrus). Word-

transfer items in the arbitrary condition activated only bilateral occipital regions. Fig. 7 and Table 3 show the results of a direct comparison between explicit and arbitrary word transfer, with significantly greater activation in the explicit-word-transfer compared to the arbitrary-word-transfer items in the posterior part of the left inferior frontal gyrus, and in bilateral occipital regions. Reading of symbol-transfer items in the explicit condition showed activation only in the left occipital cortex (Fig. 6). However, the arbitrary-symbol-transfer items activated a robust cluster of voxels in the posterior left inferior frontal gyrus (LIFG), and its right homologue. The left side cluster survived small volume correction for the anatomically predefined ROI (Table 2). In addition, the arbitrary-symbol-transfer items activated bilateral occipital, parietal and frontal regions. No clusters of activation exceeded the threshold in the direct comparison of explicit-symbol-transfer and arbitrary-symbol-transfer items (Table 3).

Regions of activation in a direct comparison between the explicit and arbitrary conditions

Condition	Region	Brodman Area	Hemisphere	z score	Voxels	x	y	z
Explicit-Arbitrary								
Trained:	no clusters							
Word Transfer:	**Inferior frontal gyrus**	9	L	3.51	27	-64	6	28
	Middle Occipital gyrus	18	L	3.5	59	-32	-92	0
	Middle Occipital gyrus	37	R	3.51	34	50	-70	2
Word Transfer:	no clusters							
Arbitrary-Explicit								
no clusters								

Table. 3 Clusters larger than 15 voxels are presented at a threshold of uncorrected $P < 0.001$. Clusters significant at a threshold of small volume corrected $P < 0.05$ are indicated in bold.

3.2.2. The implicit condition In the implicit condition both trained and word-transfer items activated the posterior part of the left inferior frontal gyrus (LIFG), in clusters that survived small volume correction for the anatomically predefined ROI (Fig. 6, Table 2). In the implicit-trained condition, activation in the posterior LIFG [À58, 8, 14] was correlated with the behavioral index for letter knowledge (word-transfer minus letter-transfer) (Z = 3.39, uncorrected P ¡ 0.001) (Fig. 8). Such correlation with letter knowledge was not found in the explicit or arbitrary training condition. However, in contrast to the explicit group, no significant difference was found in the left inferior frontal gyrus between the implicit-word-transfer and the arbitrary-word-transfer conditions. (The difference between the findings in the explicit and implicit condition may be a result of either the difference between training conditions or differences between groups). In addition, the implicit-trained items activated bilateral parietal and right occipital cortices. Implicit word transfer items activated the left occipital and right parietal cortices, and bilateral precentral gyri. Reading the symbol-transfer words in the implicit condition activated bilateral frontal gyri, and bilateral occipital regions (Fig. 6 and Table 2).

Regions of activation in comparisons across conditions

| Condition	Region	Brodman Area	Hemisphere	z score	Voxels	x	y	z
Artificial script-Latin letter-strings:	*** Inferior/middle occipital gyri/ fusiform gyrus/cerebellum**	17/19/37	L	Inf	5060	-28	-96	-18
	* Inferior/middle occipital gyri/ fusiform gyrus/cerebellum	19/37	R	Inf	5693	36	-90	-16
	* Superior parietal lobule	7	R	6.97	608	22	-82	54
	* Paracentral lobule/postcentral lobule	6/3	R	6.06	878	4	-34	60
	* Precentral gyrus	6	L	5.15	97	-58	2	48
	* Superior parietal lobule	7	L	4.7	114	-24	-80	56
	Insula	13	R	3.89	46	38	-14	8
	Precentral gyrus	4	R	3.71	39	48	-22	66
Transfer-transfer:	No clusters of activation							
Transfer-trained:	Precuneus/sup parietal lobule	7	R	3.47	32	16	-84	52
	cerebellum	-	R	3.59	47	50	-44	-34

Table. 4 Clusters larger than 15 voxels are presented at a threshold of uncorrected $P < 0.001$. Clusters significant at a threshold of whole-brain corrected $P < 0.05$ are indicated in bold and a star.

3.2.3. Effects of practice across conditions The presentation of the Latin letter-string (for which the matching response was required) was modeled separately in the analysis. Fig. 9 and Table 4 show regions activated in a comparison of the artificial script to Latin letter-strings. Greater activation for artificial script compared to Latin letter-strings was found in the bilateral superior parietal lobules (SPL), as well as bilateral fusiform and inferior occipital gyri, right paracentral and left precentral gyri. Fig. 10B shows that activation in the right SPL for Latin letter strings was decreased even compared to baseline.
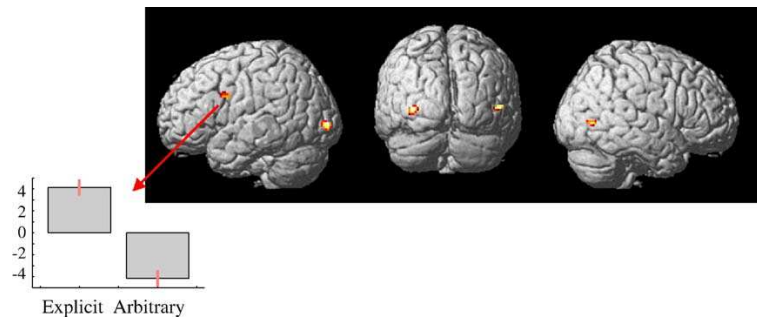
Fig. 7 Brain regions showing more activation in the explicit-word-transfer compared to the arbitrary-word-transfer condition, with the signal change in the posterior LIFG.

The comparison of trained and transfer items, across training conditions (alphabetical and arbitrary), revealed greater activation for the transfer as compared to the trained items in the right SPL (Figs. 10A, B), however, this cluster did not survive the threshold of corrected $P < 0.05$. Nevertheless, the activation in the bilateral SPL [28, À58, 58] and [À20, À64, 54] during the reading of the transfer items was correlated with performance in the transfer conditions ($Z = 4.51$ and 4.91, respectively, whole-brain corrected $P < 0.05$, Fig. 11). Performance of trained items was not correlated with the activation in the SPL.
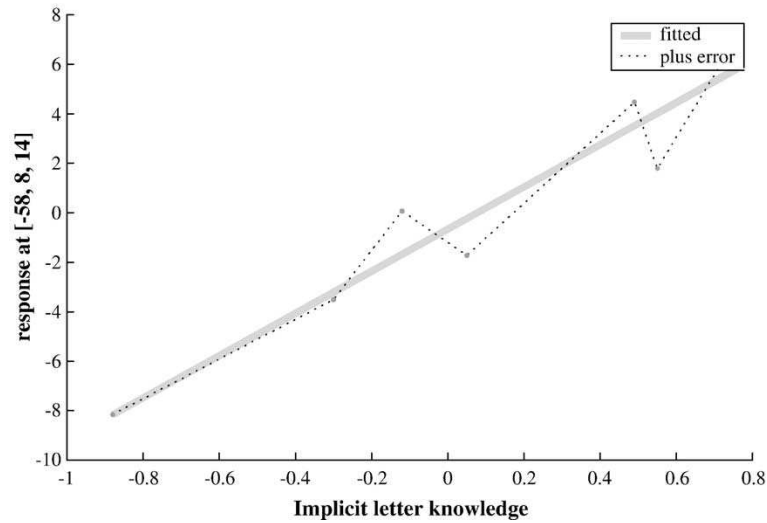
Fig. 8 The correlation of activation in the posterior LIFG during reading of Implicit-trained-words, with the individual's level of letter knowledge in the implicit condition (measured by the difference: word-transfer-letter-transfer).

4. Discussion

The results of the current study show that the amount of experience afforded for a specific set of stimuli is an important factor, interacting with the type of script (alphabetical *vs* non-alphabetical) and the type of instructions (explicit *vs* implicit) in determining the involvement of different cortical regions in reading. More experience resulted in lesser recruitment of the right SPL in: (a) all transfer conditions compared to the trained conditions, and (b) in the artificial script compared to Latin letter strings. Activation in the posterior left inferior frontal gyrus (LIFG) was affected by experience in interaction with the type of script and the type of instruction. The posterior LIFG was more active in the explicit-word-transfer compared to the arbitrary-word-transfer conditions, suggesting it is involved in segmentation and letter decoding. Our results further show that while the posterior LIFG was not active in explicitly trained words, activation was evident in the implicit condition, in both trained and word-transfer items. Moreover, the posterior LIFG and its right homologue were also activated in the arbitrary-symbol-transfer condition.
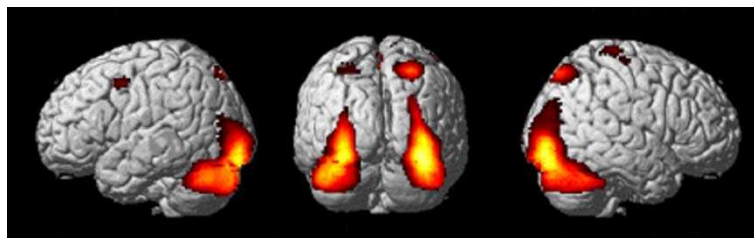
Fig. 9 Brain region showing more activation during the presentation of the artificial script as compared to Latin-letter-string.
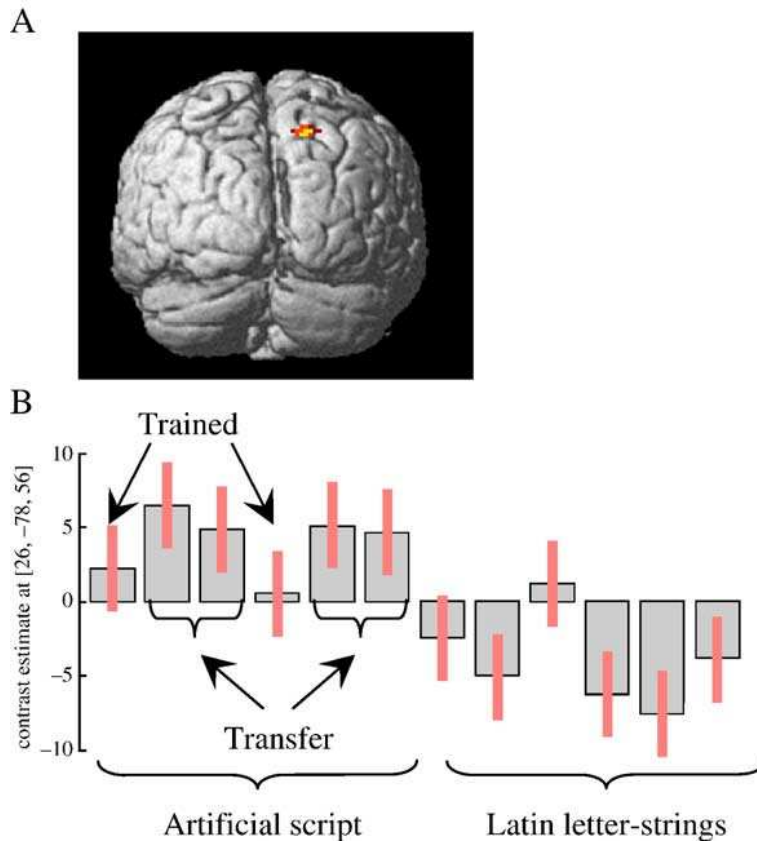
Fig. 10 (A) Brain regions showing more activation in the transfer compared to the trained items across all training conditions. (B) Signal change in the right superior parietal lobule.

4.1. Practice effects in the SPL   Previous studies suggest that the SPL is involved in coordination of spatial attention [90]. The right SPL was depicted in studies of mirror reading in English [2,54,72] and Japanese [28], suggesting its involvement in the visuospatial processing of new words. These findings are consistent with the activation of the SPL in reading our Morse-like script, which presumably relies mainly on the identification of the spatial sequencing of symbols.

The reduction in activation in the right SPL in trained items compared to transfer items, and in Latin letter-strings compared to artificial script, suggests that activation in the SPL decreased with the familiarity of the stimulus. Activation in the bilateral SPL was correlated with the individual's accuracy of performance only in transfer items, supporting the hypothesis that the SPL was required for processing transfer items more than for processing trained items. Previous studies showed decreased activation in the right SPL following training on a mirror reading task [54,72]. Two studies that compared brain activation patterns during the reading of Chinese alphabetical script (Pinyin) and Chinese non-alphabetical characters [17,41] found more activation in the right SPL for reading the less experienced Pinyin script. One may reasonably speculate that in the current study, less familiar items required the allocation of more attention to the visual search for the distinctive features compared to more familiar items. An alternative interpretation for the difference between Latin letter-strings and the artificial script in

the SPL may be the difference in the visual characteristics of the stimuli, or the fact that the artificial script stimuli were presented before the Latin letter-string, and may have activated working memory processes. However, these interpretations cannot account for the differential activation in the SPL between trained and transfer items.
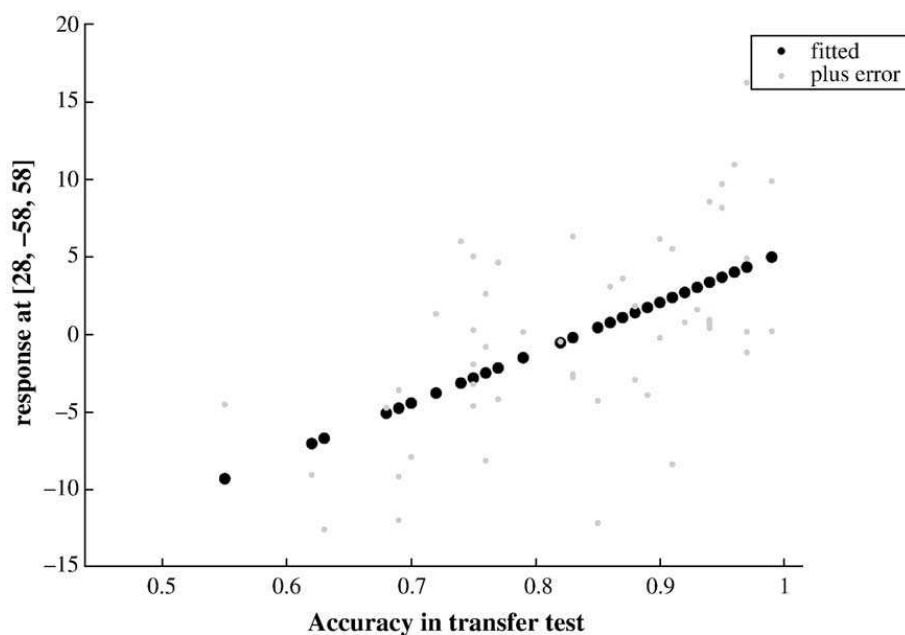
Fig. 11 The correlation of activation in the right SPL during reading of transfer items, with the individual's performance level in the transfer test.

Altogether the pattern of activation in the right SPL represents two apparently conflicting trends. While activation in transfer items increased with the individual's accuracy of performance, activation in trained items decreased in spite of the higher accuracy of performance in trained compared to transfer items. These results suggest that training may have induced unique qualitative changes in task performance, and presumably a reliance on different processes, which could not be achieved without practice, even in highly competent individuals. Similar notions of switching in processing modes during different stages of experience have recently been posited in a number of tasks [56,73,82].

4.2. The LIFG in the explicit and arbitrary conditions The explicit and arbitrary training conditions resulted in distinct patterns of brain activation, consistent with our behavioral findings in the current and previous studies [6,7]. The behavioral findings showed that training in the explicit condition resulted the acquisition of letter decoding knowledge (as suggested by the advantage for word-transfer over the letter-transfer test), while training in the arbitrary condition resulted in learning of word-specific patterns of symbol repetitions and symmetries (as indicated by a high level of performance in the symbol-transfer condition and an advantage of symbol-transfer over grapheme-transfer, in a previous experiment with a larger sample [7]). The fMRI results show

that while the explicitly trained items activated a limited left-lateralized region in the occipital cortex, arbitrary trained items activated broad bilateral regions, mainly in the parietal lobes. These findings are consistent with previous studies showing left lateralized activation in alphabetical scripts, compared to right and bilateral activation in the non-alphabetical Chinese script [17,83], and with studies showing bilateral parietal activation in visuo-spatial working memory [28,54,57,72,88,90]. Our findings are also consistent with previous neuroimaging studies showing differential activation for alphabetical and non-alphabetical reading in natural script [4,31,32,63].

To differentiate alphabetical from non-alphabetical reading, we specifically focused on the comparison of the explicit-word-transfer and the arbitrary-word-transfer conditions, which reflected the contribution of letter decoding to reading in the behavioral studies. The stronger activation of the posterior LIFG in the explicit-word-transfer compared to the arbitrary-word-transfer condition suggests that this region is involved in letter decoding. A number of previous studies reported the involvement of the posterior LIFG in phonological processes [10,17,32,38,46,49,50,52,76,82,85], and specifically in tasks that require grapheme- phoneme conversion [18,27,31,41,63,72]. However, the complete absence of posterior LIFG activation in reading alphabetical words, given fully available letter knowledge, suggests that the reading of explicitly trained words did not rely on letter decoding in the same way that relatively new words did. Rather, our results are compatible with the proposal that sufficiently familiar alphabetical words were presumably identified mainly through word-specific recognition processes [80]. This interpretation is consistent with our behavioral evidence for some degree of word-specific knowledge in the explicit condition in addition to letter knowledge.

The activation in the posterior LIFG (and its right homologue) was also evident in the arbitrary-symbol-transfer condition, suggesting that the function of the posterior LIFG may be broader than the above notion of phonological decoding. Behaviorally, both the word-transfer in the explicit condition, and the symbol-transfer in the arbitrary condition showed an intermediate level of skilled performance (with higher performance in trained items, and lower performance in the other transfer conditions). This level of performance suggests that subjects were able to analyze and decode the symbol-strings, presumably according to their knowledge about regularities within the trained items. Thus, we propose that the posterior LIFG was activated in these conditions, perhaps, because they required the segmentation of the symbol-string into familiar subunits (either letters or clusters of symbol patterns). In addition, both conditions may have involved the mapping of the segmented subunits onto other representations—either letters onto phonemes in the explicit-word-transfer condition, or new symbols onto trained symbols in the arbitrary-symbol-transfer condition.

Previous studies have shown learning related changes in the activation of the posterior LIFG in the artificialgrammar-learning paradigm [34], that presumably requires

learning of the mapping of untrained letters onto trained letters [11,19,65,69,75]. Moreover, the posterior LIFG was found to be involved in the acquisition of grammar rules of an artificial language [85] as well as in processing syntax and grammar in patients with Broca's aphasia [39,45,55,81,84]. These findings are consistent with our proposal that the posterior LIFG (and probably its right hemisphere homologue) is involved in the analysis, segmentation and decoding of regularities within a sequence, and mapping of one type of subunits to another. Phonological segmentation and grapheme -phoneme mapping may, therefore, constitute just one aspect of this broader function.

Although the greater activation in the posterior LIFG in the explicit-word-transfer compared to the arbitrary-word transfer is associated with a higher level of accuracy in the scanner, the pattern of activation in other conditions suggest that activation in the posterior LIFG does not reflect a general effect of low task difficulty. For example, high accuracy in explicit-trained items (comparable to the explicit-word-transfer) was not associated with activation in the LIFG. Moreover, despite comparable levels of accuracy in the arbitrary-symbol transfer and explicitsymbol-transfer conditions, only the former showed activation of the posterior LIFG. An alternative interpretation for the activation of the posterior LIFG in the explicit-word-transfer and arbitrary-symbol-transfer conditions is that the phonological/articulatory representation of the target word was retrieved as a preparation for production [24]. However, this interpretation must assume that the articulatory representation was retrieved although voiced response was not required, but only in some conditions.

4.3. Interaction of alphabeticality and skill in trained items Despite the lack of activation in the LIFG in explicittrained items, our results show a different pattern of activation in explicitly trained words and in arbitrary trained words. In addition to the differential reading process (letter decoding *vs* word-specific recognition), the distinct pattern of activation may be the result of different levels of skill in the reading process in the explicit and arbitrary trained items. Despite the equivalent amount of training and equivalent level of accuracy achieved by the end of training, our behavioral results suggest that reading in the explicit condition has reached a more advanced level of skilled reading, as reflected in higher preservation of learning gains in the explicit condition compared to the arbitrary condition, both in the long-term and between the training sessions [7]. The higher skill level in the explicit condition resulted, presumably, from the different number of repetitions on letters compared to words in the trained stimuli (each letter appears in 6 different words). We proposed that training in both conditions resulted in the formation of proceduralized routines for reading, with, however, the word recognition routine evolving at a slower rate compared to the letterdecoding routine. The less extensive activation in posterior visual and perceptual regions, in explicit-trained compared to the arbitrary-trained items, may be the result of the more "automatic"

routine in the explicit condition. This interpretation is consistent with findings of more extensive activation in reading a less skilled script, regardless of the alphabeticality of the language [16].

4.4. Implicit *vs* explicit instructions   The pattern of activation in the implicit condition showed similarities to the patterns of activation evoked by both the arbitrary and explicit conditions. The implicit condition was similar to the arbitrary condition in showing robust bilateral activation. Furthermore, in similarity to the arbitrary condition, all types of items in the implicit condition showed activation in parietal regions along the intraparietal sulci, suggesting the involvement of visuo-spatial processing [54,57,72,88]. In addition, both the arbitrary and implicit conditions showed robust cerebellar activation. This finding is consistent with previous studies showing cerebellar involvement in mirror reading [71] as well as in orthographic, phonological and semantic processing in natural script [33,42,92].

In similarity to the explicit condition, the implicit word-transfer condition showed activation in the left posterior IFG, suggesting some reliance on letter decoding in reading (in light of the above interpretation of the explicit *vs* arbitrary comparison). However, in contrasts to the explicit condition, activation in the left posterior IFG was evident also in implicit-trained items, suggesting that letter decoding in the implicit condition persisted even in reading trained words. Moreover, activation in the left posterior IFG during reading of implicit-trained items was correlated with the individual's effective letter knowledge (measured behaviorally as the difference between word-transfer and letter-transfer ratios). This finding supports the interpretation that the activation in the left posterior IFG in reading alphabetical words is associated with letter knowledge, and the conclusion that reading implicit-trained items involved letter decoding. Altogether, the pattern of activation in the implicit condition suggests that learning involved wordspecific pattern recognition, as well as letter decoding. However, the acquisition of letter knowledge may have been less effective in the implicit compared to the explicit condition, resulting in the reliance on letter decoding, even for reading implicit-trained items.

In the current study, no significant difference in accuracy was found between word-transfer and letter-transfer in the implicit condition, however, in similarity to the explicit condition, performance in the implicit condition was more accurate than in the arbitrary condition. This mixed pattern of results may suggest the acquisition of letter knowledge in a small number of participants or a minimal level of letter knowledge in the entire group. The small sample and large variability among individuals prevent a clear conclusion. However, the mixed pattern of activation in the implicit condition is consistent with the behavioral findings of our previous study [7]. The implicit condition resulted in wordspecific recognition knowledge in all participants, in addition to letter

knowledge in some individuals, that was, however, less effective than the explicitly instructed letter knowledge [7]. It may be hypothesized that the mixed learning of both word and letter units in the implicit condition resulted in less intensive practice on the letters, and less effective letter knowledge. Thus, our behavioral as well as our brain activation findings suggest that letter decoding acquired in the implicit condition was less effective than that acquired in the explicit condition. Previous studies have also found different patterns of brain activation in explicit and implicit training conditions [1,44,48,74]. However, rather than reflecting the difference in "awareness", we propose that the different patterns of activation in explicit and implicit training in the current study reflect the differential amounts of practice on the relevant units (letters).

4.5. Fusiform and supramarginal gyri Many studies that investigated single word reading reported activation in the fusiform gyrus, which was associated with the recognition of the orthographic pattern of familiar words prior to lexical access [4,9,17,25,26,31,64,77]. In the current study, we did not observe any consistent activation in the fusiform gyrus area. This lack of activation may be the result of insufficient training received in the current study, which is presumably required to induce a representation in this part of the cortex, typically associated with visual processing of highly familiar object categories in experts [26,31,43].

A number of word reading studies showed activation in the left angular and supramarginal gyri (SMG), claimed to be associated with mapping of orthography to phonology [9,32,41,59,76]. In the current study, these regions were not activated in the explicit-word-transfer condition that presumably entailed grapheme -phoneme conversion. Rather, the angular gyrus and SMG were activated bilaterally in the arbitrary-trained and arbitrary-symbol-transfer conditions, which do not afford letter decoding. An alternative interpretation of the results, that may account for the activation of the SMG in the arbitrary rather than in the explicit condition, is that letter decoding in the explicit condition involved mapping from the artificial letters to Latin letters, rather than mapping of letters to phonemes. In spite of the efforts to enhance the association of letters to phonemes by requiring the pronunciation of the target words and letters, participants may have reverted to mapping artificial letters to familiar Latin letters in the explicit condition. This shortcut may have been too demanding in the arbitrary condition due to the higher visual complexity of whole words, resulting in mapping of orthography to phonology in the arbitrary condition. Hence, it may be suggested that the SMG was activated in the arbitrary and not in the explicit condition since it is involved in the conversion of orthography to phonology regardless of the size of the units (i.e., letters or words). The posterior LIFG, on the other hand, may be involved in the segmentation and mapping of units, regardless of their modality, and hence it was activated in the explicit-word-transfer and arbitrarysymbol-transfer conditions.

5. Conclusions

Our results suggest that the posterior LIFG is involved in letter decoding as part of its broader function in segmentation and decoding of sequences. The results provide a neural support for the notion that reading of well-trained alphabetical words does not rely on letter decoding. Nevertheless, our results suggest that even when reading of trained alphabetical words is done with minimal recourse to letter decoding, it may still elicit a different pattern of activation from reading non-alphabetical words because of a difference in the evolution of the reading routine. Consistent with our behavioral findings, the fMRI results suggest that implicit training on alphabetical words resulted in less effective letter knowledge, with letter decoding persisting even to the reading of trained words. The critical effect of the amount of practice was also demonstrated in the pattern of activation in the right superior parietal lobules. Our results showed that the individual's level of competence in reading relatively novel artificial script words, and their amount of experience with reading specific trained words, have independent and opposite effects on the activation in the right SPL. This finding further emphasizes the unique effect of experience, which continues to shape performance even in competent readers. Altogether, our findings suggest that the neural processes involved in reading a given word and the pattern of brain activation elicited by its presentation are determined by the interaction of the alphabeticality of the word, the type of instruction received by the reader during the acquisition of reading (explicit or implicit) and the amount of practice afforded for the specific word.

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Auditory processing abnormalities in schizotypal personality disorder: An fMRI experiment using tones of deviant pitch and duration*

Abstract

Background: One of the cardinal features of schizotypal personality disorder (SPD) is language abnormalities. The focus of this study was to determine whether or not there are also processing abnormalities of pure tones differing in pitch and duration in SPD. **Methods:** Thirteen neuroleptic-naïve male subjects met full criteria for SPD and were group-matched on age and parental socioeconomic status to 13 comparison subjects. Verbal learning was measured with the California Verbal Learning Test. Heschl's gyrus volumes were measured using structural MRI. Whole-brain fMRI activation patterns in an auditory task of listening to tones including pitch and duration deviants were compared between SPD and control subjects. In a second and separate ROI analysis we found that peak activation in superior temporal gyrus (STG), Brodmann Areas 41 and 42, was correlated with verbal learning and clinical measures derived from the SCID-II interview. **Results:** In the region of the STG, SPD subjects demonstrated more activation to pitch deviants bilaterally ($p < 0.001$); and to duration deviants in the left hemisphere ($p = 0.005$) (two-sample t). SPD subjects also showed more bilateral parietal cortex activation to duration deviants. In no region did comparison subjects activate more than SPD subjects in either experiment. Exploratory correlations for SPD subjects suggest a relationship between peak activation on the right for deviant tones in the pitch experiment with odd speech and impaired verbal learning. There was no difference between groups on Heschl's gyrus volume. **Conclusions:** These data suggest that SPD subjects have inefficient or hyper-responsive processing of pure tones both in terms of pitch and duration deviance that is not attributable to smaller Heschl's gyrus volumes. Finally, these auditory processing abnormalities may have significance for the odd speech heard in some SPD subjects and downstream language and verbal learning deficits.

1. Introduction

Auditory sensory processing has been found to be impaired in schizophrenia (Salisbury et al., 1998; Javitt et al., 2000) and correlate with clinical features, particularly negative symptoms (Javitt et al., 2000), (Kasai et al., 2002) (Leitman et al., 2005) and cognitive impairment (Baldeweg et al., 2004). Abnormalities in the superior temporal gyrus (STG) have been implicated in the processing of pure tones, a fundamental element of complex sounds and language, using fMRI (Wible et al., 2001) and event-related potentials (Salisbury et al., 1998). Hallucinations, which may be considered an error in auditory sensory processing, have been associated with the STG (Dierks et al., 1999) (Cleghorn et al., 1992), with the STG more activated during hallucinations than actual speech (David et al., 1996). The STG has also been implicated in verbal learning deficits in schizophrenia using PET (Ragland et al., 2001). However, research in schizophrenia has been confounded by potential modulating effects of neuroleptic medications on fMRI signal (Stephan et al., 2001; Brassen et al., 2003). Neuroleptic-naïve subjects are needed to ensure that research findings are due to underlying neuropathology rather than iatrogenic effects. Subjects with schizotypal personality disorder (SPD) may provide an ideal population of neuroleptic-naïve subjects for fMRI studies. Although SPD shares many features with schizophrenia, it is not a direct proxy for schizophrenia, as SPD subjects are not psychotic. Nonetheless, SPD and schizophrenia have traditionally been considered part of the schizophrenia spectrum disorders based on epidemiological data (Kety et al., 1967) (Kendler et al., 1993), shared clinical features such as thought disorder (Dickey et al., 1999) and paranoia (Dickey et al., 2005), similar biological markers (Siever and Davis, 2004), comparable cognitive deficits in verbal learning (Voglmaier et al., 1997) (Voglmaier et al., 2000) (Voglmaier et al., 2005), and overlapping morphometric abnormalities (Dickey et al., 2002a,b).

Indeed, one brain region critical for early sensory auditory processing, Heschl's gyrus (Yoo et al., 2005), has been shown to have reduced volumes in subjects with SPD (Dickey et al., 2002a,b), similar to what has been shown in schizophrenia (Hirayasu et al., 2000). Heschl's gyrus lies on the plane of the STG, a region found to have small volumes in males with SPD (Dickey et al., 1999; Downhill et al., 2001), and in females with SPD with a family history of mental illness (Dickey et al., 2003). Of particular interest to this report, however, Heschl's gyrus is noted to have marked intersubject morphometric volume and shape variability (Leonard et al., 1998; Knaus et al., 2006), thus complicating the interpretation of volume data (Knaus et al., 2006).

As in schizophrenia, abnormalities of auditory processing at multiple stages have been shown in SPD including the P50 (Cadenhead et al., 2000), P300 (Salisbury et al., 1996), and N400 (Niznikiewicz et al., 1999). Similarly, in subjects with high scores of schizotypal features but not frank SPD, auditory abnormalities have been shown in the P300b (Klein et al., 1999), N400 (Kimble et al., 2000), and in phonemic discrimination

(Li et al., 2003). Finally, in one paper examining mismatch negativity (MMN) in subjects clinically diagnosed with schizotypy but for whom a formal diagnostic interview was not performed, schizotypal subjects were found to have increased amplitudes in the Fz and Cz electrodes to pitch deviants (Liu et al., 2007). Hence, it appears that in the schizophrenia spectrum there is a range of auditory processing abnormalities, albeit with some negative findings (Brenner et al., 2003). The current report seeks to build on this literature by examining tone processing of pitch and duration deviance in SPD subjects using fMRI.

One question in the literature is how to best measure deficits in early auditory sensory processing in schizophrenia and SPD, whether through event-related potential (ERP) or fMRI studies. The ERP methodology affords good temporal resolution while fMRI offers a good spatial resolution. ERP components often used to examine processing auditory pre-attentive and attentive abnormalities in schizophrenia are mismatch negativity (MMN) and P300. A MMN ERP paradigm, which elicits an early negative deflection following a deviant stimulus, results in a less negative deflection in schizophrenic subjects and has been used frequently to assess subjects' pre-attentive ability to detect changes in tone features (e.g.:Salisbury et al., 1998). In contrast, to our knowledge (Medline search 1/10/08), there have been only two published fMRI experiments utilizing the mismatch design in patients with schizophrenia (Wible et al., 2001; Kircher et al., 2004). Adequate numbers of deviants are required to produce a detectable contrast-to-noise ratio, yet this must be balanced with experimental length, as subjects' tolerance to long scanning session is limited. For these reasons, we employed a significantly modified mismatch experiment with larger differentials between standard and deviant tones and more frequent deviants as compared with prototypic mismatch paradigms.

Therefore, whether the STG in SPD exhibits normal functioning as measured by hemodynamic response to early auditory sensory information is the central question driving the current report. Structural MRI and neuropsychological testing procedures are also included. The possible relationship between early auditory processing and downstream language and other cognitive functions, as well as the highly complex clinical manifestations of SPD, is also evaluated in an exploratory fashion. These questions are important to ask in SPD subjects as they are neuroleptic-naïve, thus, a complicated confound in similar studies of auditory function with schizophrenic subjects is removed (Umbricht et al., 1998).

2. Methods

2.1. Subject recruitment   All subjects were male; right-handed; between 18 and 55 years old; neuroleptic-naïve; on no psychotropic medications; had no history of ECT, neurologic disorder, substance abuse in the last 1 year or substance dependence in the

last 5 years; and were recruited from the community through newspaper and subway advertisements (for recruitment specifics, see Dickey et al., 2005). Note that data for past psychotropic use of any kind or substance dependence beyond five years ago was not available. SPD subjects met DSM-IV criteria for SPD using the SCID and SCID-II interviews and had no personal history of bipolar disorder nor psychosis. Thirteen SPD subjects were group-matched on age, parental socio-economic status, and estimated IQ to 13 comparison subjects who had additional exclusionary criteria of no personal history with Axis I or Axis II disorder as determined by SCID, or first-degree relative history of Axis I disorder.

2.2. Clinical measures   SPD criteria were from SCID-II interview. IQ was assessed through the WAIS-R Vocabulary and Block Design sub-scales (Brooker and Cyr, 1986). Verbal learning was assessed using the California Verbal Learning Test (CVLT), total words learned trials 1-5 (Delis et al., 1987). This test was selected as a test of verbal working memory and because it has been shown by our laboratory to be abnormal in SPD subjects (Voglmaier et al., 1997; Voglmaier et al., 2000; Voglmaier et al., 2005).

2.3. Structural MRI   Heschl's gyrus was manually delineated on resolution SPGR images obtained within a year of the fMRI protocol, except one SPD subject for which no structural MRI was available. The protocol for the drawing resembled that of a previously published report on Heschl's volumes (Dickey et al., 2002a,b). The anterior boundary was the temporal stem; the posterior boundary was the complete crux of the fornix; the lateral boundary was determined by a horizontal line extending laterally from the superior most white matter track of the STG. There was one major methodological difference in the drawing between the two reports, however. In this report axial views were used initially to guide the definition of the extent of Heschl's. Axial views were not available previously. With the use of Slicer software (www.slicer. org) one could now visualize whether there was a single transverse gyrus, a common medial stem branching to two more laterally in which case both would be included per Steinmetz's criteria (Steinmetz et al., 1986), or two medial stems joining more laterally in which case only the more anterior portion would be selected. This ability to visualize and draw in three dimensions represents a significant technological advancement compared with previous capabilities and is important given the marked inter-subject and even inter-hemispheric variability of this gyrus (Knaus et al., 2006). Volumes were corrected for total intracranial contents using a regression procedure (Dickey et al., 2002a,b). Inclusion of Heschl's volume measurement was important for the interpretation of the functional data.

2.4. fMRI acquisition and post processing   Whole-brain images were acquired on a 3.0T GE system in the oblique axial plane parallel to the superior temporal plane prescribed from the localizer images. Functional image parameters included whole-brain

coverage, 30 slices, 5 mm thick with 1 mm gap, 162 acquisitions the first 6 of which were removed, FOV 24, matrix 64x64, TR 2.5, TE 35. The same prescription (orientation/slice thickness) was applied to obtain a lowresolution SPGR sequence. These low-resolution SPGR images were reoriented, realigned, and normalized to the Montreal Neurological Institute (MNI) T1 template with the resulting matrix files applied to the functional images using SPM2. Functional images were subsequently smoothed (using 12 FWHM 3-dimensional Gaussian kernel).
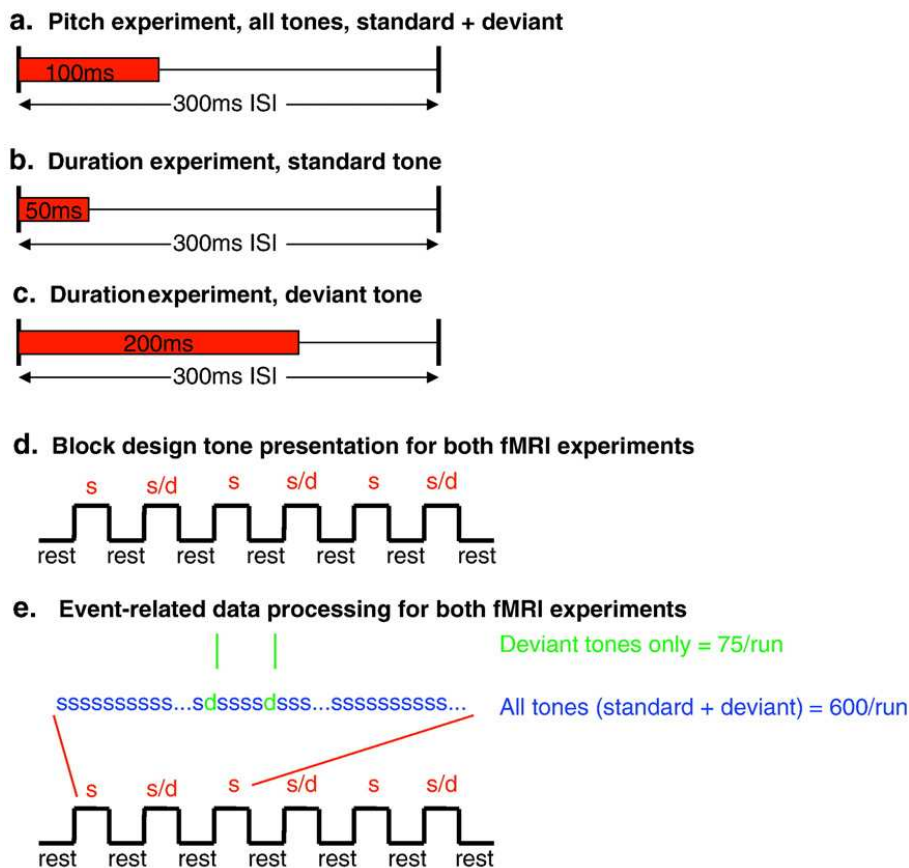
Fig. 1 Diagrams of stimuli presentation and processing. **a**. For the pitch experiment all tones are 100 ms in duration with 200 ms of silence before the next tone. **b**. For the duration experiment, the standard tone is 50 ms in duration with 250 ms of silence before the next tone. **c**. For the duration experiment the deviant tone is 200 ms in duration with 100 ms of silence before the next tone. This variation decreases the expectancy factor. **d**. Tones were presented in block design. **e**. Hemodynamic response curves were generated for all tones together (both standard and deviant, all tone condition) and for only the deviant tones (deviant condition). ISI = interstimulus interval; ms = milliseconds; s = standard; s/d = standard and deviant tones intermixed; rest = silence.

2.5. Stimuli Two experiments were employed to activate the auditory cortex, one using the pitch deviants and the second using the duration deviants. Tones were transmitted via sound-insulated and cushioned earphones (Silent Scan, Avotec, Jensen Beach, FL) at 80 db SPL (Sound Pressure Level). All tones had 10 ms rise and fall times and an interstimulus interval of 300 ms and were played at 80 db. Experiment 1: Pitch. The standard tone was 500 Hz and the deviant tone was 2000 Hz, all tones 100 ms in duration (Fig. 1a). Experiment 2: Duration. The standard tone was 50 ms in duration, the deviant tone was 200 ms in duration, with a frequency of 500 Hz for all tones (Fig. 1b and c). Presentation was block design with 30 s blocks of tones alternating with 30 s rest (Fig. 1d). Each tone block consisted of 100 tone presentations, alternating between blocks of 100% standard tones and mixed blocks of 75% standard tones and 25% deviant tones. In the mixed standard and deviant blocks the order of standard and deviant tones was randomly determined. Only one deviant (pitch or duration) was presented in a given run. Run duration was 6'46". There were two runs for pitch and two for duration for a total of four runs, order counterbalanced among subjects. Subjects heard 1050 standard tones and 150 deviant tones for a total of 1200 tones per experiment (Fig. 1e). For technical reasons, data were acquired on only 11 SPD subjects for the duration experiment, therefore, the sample size differs in the two fMRI experiments. Task for both experiments was passive listening with eyes closed. Following each run subjects were queried as to whether they heard the tones to ensure adequate hearing and wakefulness. All subjects affirmed that they did indeed hear the tones after each run. Subjects were not asked nor expected to differentiate between the tones.

Subject demographics and absolute Heschl's gyrus volumes in milliliters

	SPD	NC	p
N	13	13	
Age	36.8 (10.8)	30.4 (11.4)	<0.2
PSES	4.0 (1.2)	3.8 (1.4)	0.08
SES	3.0 (1.4)	3.2 (1.4)	0.7
IQ	116 (9.7)	120.4 (12.4)	<0.4
Education	15.2 (1.9)	18.0 (3.8)	0.02
SSPT score	55.2	56.2 (N = 8)	<0.5
Left Heschl's gyrus[a]	2.23 (0.9)	2.35 (0.6)	0.74
Right Heschl's gyrus[b]	1.95 (0.51)	1.92 (0.2)	0.29

Table. 1 Note that statistics were performed on regressed not absolute volumes in order to account for confounding effect of head size. PSES = parental socio-economic status, SES = socio-economic status, SSPT = Speech Sound Perception Test.
[a] $F(1, 24) = 0.109$.   [b] $F(1, 24) = 1.128$.

2.6. fMRI statistical methods

2.6.1. Whole-brain analysis This was the primary statistical analysis for the pitch and duration fMRI experiments. Whole-brain eventrelated procedures were employed statistically in order to single out the effect of all tones (standard + deviant), and in a separate analysis, the differential effect of hearing only deviant tones. Restated, the hemodynamic responses were modeled first in order to examine the effect of being in the scanner and hearing all tones, both standard and deviant, regardless of block type (main effect) (Fig. 1e, in blue and green). Subsequently, the hemodynamic effect of hearing only deviant tones (parametric effect) was modeled (Fig. 1e, in green). This isolates the effects of hearing deviant tones "on top of" the effect of hearing all tones, that is, standard and deviant (green only "on top of" green and blue). Specifically, the main effect of hearing all tones (standard + deviant, regardless of block) *vs* rest were modeled using one regressor (effect of hearing deviant tones only) in the General Linear Model for each subject. Second, the differential effect of hearing the deviant tones was modeled as a parametric regressor (deviant tones as 1 and standard tones with value 0) in order to measure the deviant-related modulation of the BOLD signal time course for each subject. Thus the effect of hearing all tones (both standard and deviant combined, the effect of being in a scanner and hearing tones, the main effect) could be compared as well as the effect of only hearing deviant tones (parametric effect). Subject specific whole-brain contrast images from the two groups were pooled and were compared using one-sample (all tone and deviant tone conditions for both experiments) and two-sample *t*-tests (all tone and deviant tone conditions for both experiments) for the random-effects analysis. Note that these analyses were whole-brain analyses.

Clinical/cognitive/functional correlations

	Condition	ROI	RHO	p
SPD criteria of odd	Pitch	Right 41	0.639	<0.02
thinking or speech		Right 42	0.534	<0.06
CVLT	Pitch	Right 41	-0.633	<0.03
		Right 42	-0.670	<0.02
		Right STG	-0.830	0.001

Table. 2 Correlations between peak *t*-activation values for the ROI, namely, STG, Brodmann Areas 41 and 42, with clinical criteria, and verbal learning (CVLT) are given.

2.6.2. Secondary ROI analysis In order to perform exploratory correlations with clinical/cognitive measures, a second procedure, a second analysis, a voxel-wise restricted ROI analysis, was employed in order to isolate peak activation in the region

of the STG for individual subjects. Note that this secondary ROI analysis was used for correlations only and that the main fMRI analysis used a whole-brain analysis. Therefore, for secondary and exploratory correlations, ROI were selected as defined by WFU PickAtlas (www.fmri.wfubmc.edu). Specifically, PickAtlas defined ROI masks were applied and peak t-values were generated for left and right Brodmann Areas 41, 42, and STG for the deviant condition (three regions of interest (ROI) per side per experiment, 12 in total). These regions were selected a priori as they likely are the regions involved in tone processing (Yoo et al., 2005; Kropotov et al., 1995; Alho, 1995). Note that Brodmann Area 41 derived from PickAtlas does not directly correspond to the manual Heschl's drawing above. They are slightly different measurements but both roughly correspond to presumed areas of pure tone processing. Threshold was set at 0.05 corrected.

2.7. Clinical/cognitive/functional correlations Exploratory Pearson correlations with peak t-values and clinical measures were obtained. The clinical measures that included the nine SPD diagnostic criteria and CVLT were correlated with the 12 ROI for a total of 120 correlations. To limit the number of correlations considered significant post hoc, only those which were significant in two of the three regions per side in a single condition were accepted (one of the two regions could have a correlation significant at the trend level). For example, a significant correlation with a clinical measure and right Brodmann Areas 41 and 42 would be accepted, but not right 41 and left 42, nor just right 41. We appreciate that even with these more stringent rules, a large number of correlations were performed. However, given that this is the first fMRI paper on auditory processing in SPD to our knowledge (Medline search performed 1/10/08), an attempt to understand the clinical significance of the potential findings was important.

3. Results

3.1. Subject demographics There were no group differences in age, parental socio-economic status (PSES) (scale 1-5, with 5 as highest PSES), personal socio-economic status (SES), or IQ although SPD subjects had fewer years of education (Table 1). SPD subjects met criteria for additional co-morbid personality disorders including: avoidant (N = 1), paranoid (N = 6), borderline (N = 2), obsessive compulsive (N = 3), narcissistic (N = 2), passive aggressive (N = 1), and schizoid (N = 1), similar to what others (McGlashan, 1986) and our laboratory previously published (Dickey et al., 2005) with the exception of a higher percentage of paranoid subjects here (46%). The mean number of DSM-IV SPD criteria met for the SPD group was 5.62 (S.D. = 0.768) out of a possible nine criteria.
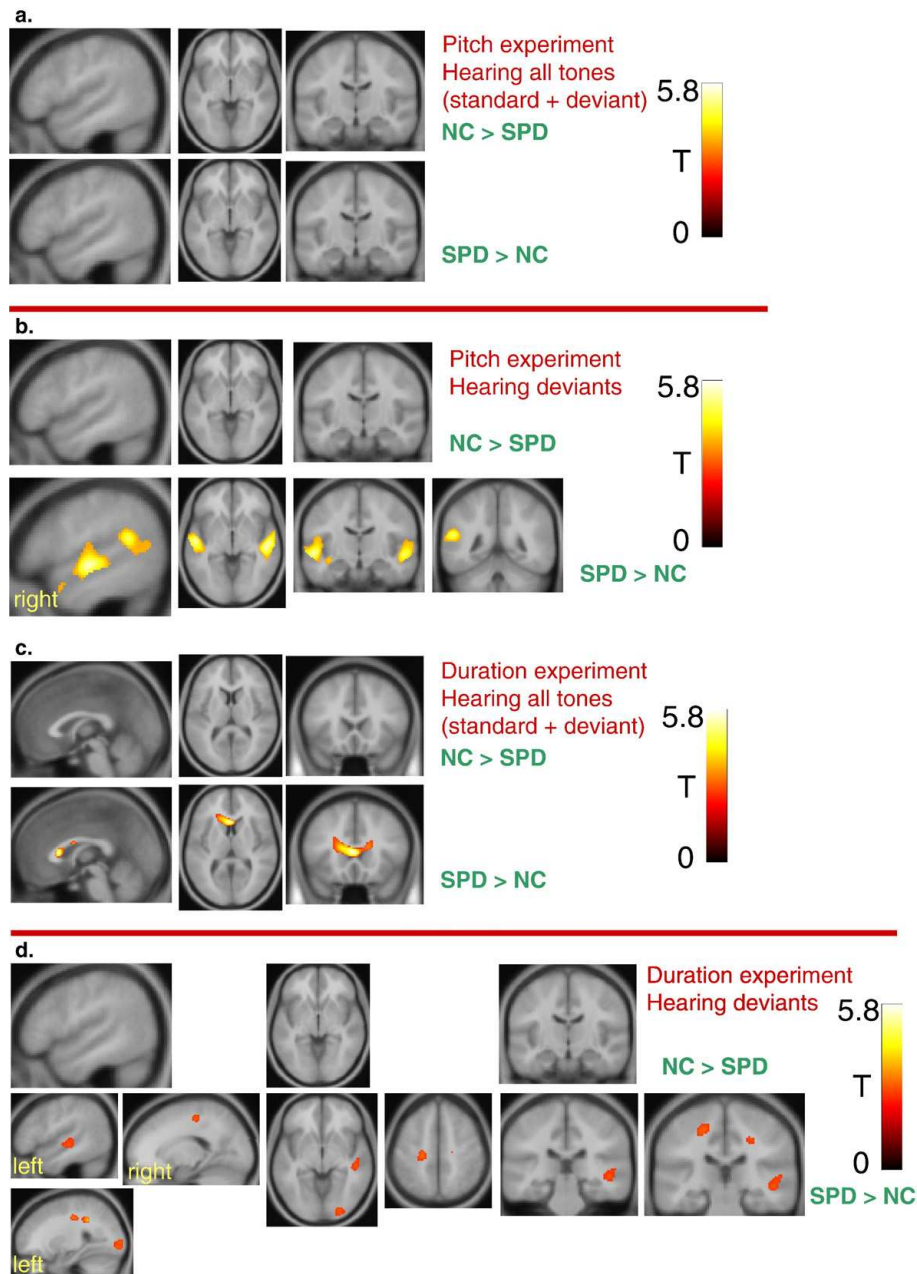
Fig. 2 Whole-brain statistical parametric maps with consistent p scale shown. Note that regardless of experiment (pitch or duration) and regardless of tone set heard (all tones or deviants only), there is no area of the brain in which control subjects activated more than SPD subjects. **a**. Pitch experiment, all tones (standard + deviant) heard analyzed together. **b**. Pitch experiment deviant condition. Note significantly more activation in SPD subjects compared with control subjects in the region of the STG bilaterally. Thresholded at the $p < 0.001$ level with an extent of activation cluster size limit set at 240 voxels. MNI coordinates and cluster significance by two-tailed t-tests were: (-52, -22, -2, $T = 5.3, p < 0.001$), (54, -46, -2, $T = 5.3, p < 0.001$), (54, -46, 18, $T = 4.85, p < 0.001$). **c**. Duration experiment, all tones (standard + deviant) condition. Thresholded at the p b 0.01 level with an extent of activation cluster size limit set at 0 voxels to ensure all visible super-threshold activation. MNI coordinates and cluster significance by two-tailed t-tests were: (2, 22, 10, $T = 5.67, p < 0.0005$) and (-14, 4, 24, $T = 5.3, p < 0.0005$). **d**. Duration experiment, deviant condition. SPD subjects activated more to deviant tones than comparison subjects in left temporal and bilateral parietal regions. Thresholded at the $p < 0.01$ level with an extent of activation cluster size limit set at 240 voxels for temporal lobe regions, 0 voxels for parietal regions in order not to lose relevant findings in that area. MNI coordinates and cluster significance by two-tailed t-tests were: for temporal lobe regions, (-48, -28, -4, $T = 2.83, p = 0.005$ and -22, -88, 2, $T = 3.1, p = 0.003$); for parietal lobe regions, (-26, -42, 38, $T = 4.0, p < 0.001$), (-24, -20, 42, $T = 3.2, p = 0.002$), (28, -40, 38, $T = 3.36, p = 0.001$). Note standardized color bars across images reflect relative T scores. Neurological convention (left is left).

3.2. Heschl's volumes There were no group differences in left or right Heschl's gyrus gray matter volumes manually drawn on high-resolution SPGR images and corrected for intracranial contents using a regression procedure (Dickey et al., 1999) (Table 1). Indeed the effect size on the left was small, effect size = 0.18, the effect size on the right was 0.03. The lack of volume difference, however, strongly suggested that differences in functional activation were not due to a primary volume difference.

3.3. Pitch experiment There were no areas in which comparison subjects demonstrated statistically significantly more activation than SPD subjects in neither the all tones (standard + deviant) condition nor the deviant tone condition. For the differential effect of deviance, there were three areas in which SPD subjects demonstrated more activation (two-sample t-test) all in the region of the STG bilaterally (Fig. 2a and b).

3.4. Duration experiment There were no areas in which comparison subjects demonstrated statistically significantly more activation than SPD subjects in neither the all tones (standard + deviant) nor the deviant tone condition. For the additive effect of hearing deviant tones only, there were areas of significantly more activation in both the temporal and parietal lobes in SPD subjects compared with controls (Fig. 2c and d).
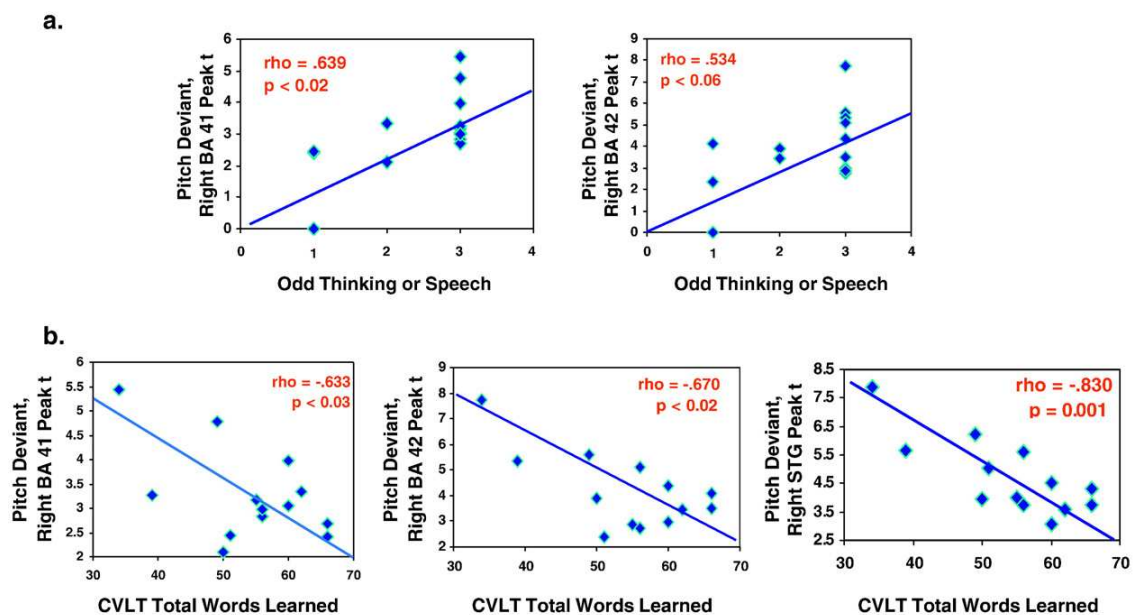
Fig. 3 Scatterplots of peak activation and clinical and cognitive measures. **a**. SPD subjects with greater impairment due to odd thinking or speech (higher score) demonstrated more activation while passively hearing tones in BA 41 and 42 on the right. **b**. SPD subjects who learned fewer words on the CVLT had greater peak activation in the right BA 41, 42, and STG. BA = Brodmann Area.

3.5. Clinical correlations with fMRI activation patterns in the duration experiment Of note, correlations were found on the right side between the clinical symptom of odd thinking/speech in the pitch experiment (Table 2). The more abnormal

the activation (t-score) while hearing deviant pitch tones, the more the impairment due to the clinical symptom. Verbal learning, a key abnormality in SPD, correlated with all right-sided regions such that the fewer words learned in trials 1-5, the more abnormal the activation while hearing deviant pitch tones. The number of correlations performed was high given the exploratory nature of the study and results would not have withstood a Bonferroni correction. However, they are included here to generate future hypotheses regarding the functional/anatomic relationships in SPD. As stated in the Methods section, included in Table 2 are only those correlations which were found in at least 2/3 regions/side (Fig 3).

4. Discussion

The main finding of this report is increased activation in the region of the STG bilaterally in SPD subjects compared with controls while subjects heard deviant tones regardless of whether the deviance was in the pitch or duration. In the whole-brain analysis, in no region of the brain did comparison subjects activate more than SPD subjects. These findings suggest that SPD subjects compared with controls had inefficient or hyper-responsive processing of two of the most basic aspects of auditory sensory stimuli. These data cannot unequivocally address the question as to whether the SPD subjects have inefficient processing and, thus, needed to recruit more neurons to process the tones with a resulting larger hemodynamic response, or, the reverse, that SPD subjects have an exaggerated response to subtle changes in sensory inputs with a resulting larger hemodynamic response curve. More basic research is required to differentiate those two possible interpretations. Nonetheless, these current findings cannot be attributed to small Heschl's gyrus volume as the groups did not differ on that measure.

Deficits in early auditory sensory processing, including N1, MMN, and P300, have been shown using ERP in schizophrenic subjects (Baldeweg et al., 2004; Kasai et al., 2002; Salisbury et al., 1998; Javitt et al., 2000; Javitt et al., 1995; Elvevag et al., 2004), in prodromal subjects (Brockhaus-Dumke et al., 2005), and in SPD subjects (Salisbury et al., 1996; Niznikiewicz et al., 2000; Liu et al., 2007). Moreover, progressive changes in schizophrenic subjects can be indexed using a MMN paradigm in the ERP environment (Salisbury et al., 2007). Indeed, ERP has certain advantages in testing auditory sensory processing in that tones can be played in sound-proof laboratories with little to no extraneous noise, experimental design allows for a large number of deviants, greater than 160 in most studies (Shelley et al., 1991; Javitt et al., 1995; Umbricht et al., 1998; Michie et al., 2000; Baldeweg et al., 2004; Brockhaus-Dumke et al., 2005) (exception, Kirino and Inoue, 1999) and allows for precise time recordings on the order of milliseconds at the expense of poor spatial resolution.

In contrast, fMRI allows for more accurate anatomic localization at the expense of poor time resolution and high ambient scanner noise, although some have utilized

the scanner noise as stimuli (Mathiak et al., 2002; Kircher et al., 2004). Applying a prototypic mismatch paradigm has been challenging in the fMRI environment resulting in few papers on schizophrenia (Wible et al., 2001; Kircher et al., 2004). Even using scanner noise as the stimulus causes limitations as variation in pitch cannot be tested (Mathiak et al., 2002; Kircher et al., 2004).

How one might measure the effect of tone deviants also differs between ERP and fMRI. ERP MMN studies rely on traditional subtraction of waveforms (i.e.: waveforms from standard tones subtracted from waveforms from deviant tones) (Javitt et al., 1995; Umbricht et al., 1998). Unfortunately, in fMRI aberrant activation patterns can result from subtraction. These areas of unusual activation may reflect "spontaneous neuronal activity", that is, areas not predicted by task demands, which cannot be experimentally controlled (Binder et al., 1999). A mismatch task is not cognitively demanding, in fact it is arguably pre-attentive (Naatanen 1990), possibly allowing for more "task-unrelated thoughts" (Binder et al., 1999). These "task-unrelated thoughts" can result in changes in blood flow detected by BOLD method (Binder et al., 1999). In fact, the hemodynamic effect of such thoughts using the subtraction method has been demonstrated in a tone task (Binder et al., 1999). Moreover, depending on the statistical approach, subtraction or other, results can differ markedly (Friston et al., 1996). The subtraction method assumes "pure insertion", that the cognitive process is "irrespective of the cognitive or physiological context" (Friston et al., 1996), an assumption which may not be valid. Indeed, the two fMRI papers in schizophrenia compared groups on standard and deviant tones separately, thus avoiding the difficulties of the subtraction method in an fMRI environment (Wible et al., 2001; Kircher et al., 2004).

In the current fMRI study the effect of deviants was measured using a parametric analysis. Specifically, the differential processing of deviant tones against the background of hearing all tones was measured (i.e.: the first parameter is the effect of hearing all tones, both standard and deviant; and the second parameter is the effect of hearing deviant tones only) (Fig. 1e). This has the benefit of making no assumption of "pure insertion" (Friston et al., 1996) and isolates the effect of hearing deviant tones "on top of" hearing all tones. In addition, this method may possibly minimize the hemodynamic effect of "task-unrelated thoughts" (Binder et al., 1999). Another aspect of this study which differed from the MMN ERP literature was the use of disparate frequencies and durations between the standard and deviant tones. Stimuli used across studies have varied with differences between standard and deviant pitches as small as 24 Hz (1000-1024 Hz) (Javitt et al., 1995) to as large as 1000 Hz (1000-2000 Hz) (Kirino and Inoue, 1999) and differences in duration as small as 25 ms (25-50 ms) (Baldeweg et al., 2004). Nonetheless, the presence of the MMN-like deflection in both conditions suggests that these experimental parameters engage the early auditory sensory processing stream. Indeed, stimulus presentation features including probability and degree of separation of

the deviants, and interstimulus interval, are all important variants which may affect the results (Michie et al., 2000). However, as SPD has demonstrated less severe abnormalities than schizophrenia on electrophysiological measures (Trestman et al., 1996), more extreme differences in terms of pitch and duration between the standard and deviant tones were selected to amplify the fMRI signal. Moreover, a larger differentiation between standard and deviant tones would help to compensate for any potential deficit in tone discrimination processing described in the schizophrenia literature (Javitt et al., 2000; Leitman et al., 2005). Although a lower percentage of deviant tones would have similarly increased an electrophysiological signal (Javitt et al., 2000), in order to achieve enough trials for an adequate hemodynamic response, a higher percentage of deviant tones was selected.

Although the paradigm used in this study is not standard mismatch, evidence from the MMN literature may inform the current findings. For example, generators for the MMN are thought to be from the auditory cortex (Kropotov et al., 1995) with physical separation of foci for processing of pitch and duration (Molholm et al., 2005), similar to the current findings. Some workers have also noted activation from frontal generators thought to reflect a shift of attention toward the deviant, although recent work suggests that the role of the frontal generator may not depend on attention requirements (Shalgi and Deouell, 2007). Indeed, a recent review by Naatanen et al. (2007) suggests that frontal activity may be due to the sum of supratemporal generators (Naatanen et al., 2007). Our report did not find evidence of fMRI activation in either group in the frontal lobe, possibly due to the use of largely disparate standard and deviant tone features (Shalgi and Deouell, 2007). The activation of the parietal lobe in the duration experiment is consistent with the hypothesis that the parietal lobe is important for time perception (Harrington et al., 1998) and change-detection (Molholm et al., 2005). Indeed, bilateral activation has been demonstrated with deviants in duration (Molholm et al., 2005). Finally, abnormalities in MMN have been documented in clinically diagnosed patients with SPD (Liu et al., 2007).

In this report, in contrast to our previous report (Dickey et al., 2002a,b), we did not show any difference in Heschl's gray matter volume. We would argue, however, that, in general, in the peri-Heschl's/ STG region, SPD subjects likely have smaller volumes (Dickey et al., 2002a,b, 2003, 1999; Downhill et al., 2001 {Koo, 2006 #3366}). There are several differences between our two reports on Heschl's gyrus ((Dickey et al., 2002a,b) and current) and that volumes measured depend on many factors including subject demographics, co-morbidity, subject N, image viewing tools which can affect landmark detection, and inter-subject and inter-hemispheric variability of Heschl's morphology, particularly in schizophrenia spectrum disorders. First, in the earlier report there was a significant difference between IQ and personal socio-economic status between groups suggesting that cohort may have represented a more impaired group of SPD subjects.

Second, and delving deeper into the issue of subject characteristics, the percentage of subjects meeting DSM-IV criteria for other Axis II disorders differs between samples. In the prior report there were more borderline personality disorder subjects (31% *vs* 15% in current sample) and fewer who met criteria for paranoid personality disorder (37.5% *vs* 46% in current report). Little is known about brain morphology of the STG region in paranoid and borderline personality disorders (no papers found per PubMed search performed 4/17/08). Whether the presence of co-morbid personality disorders has an effect on Heschl's measurement cannot be addressed. Third, in this current sample, the subject N is smaller, leading to possibly less stable data. Fourth, the current study used Slicer as the image processing software tool, a more sophisticated tool than previously available (www.slicer.org) as this tool now allows for simultaneous 3D viewing. As noted under the Methods section above, the delineation of Heschl's previously may have included more peri-Heschl's area posteriorly thus leading to the differences between groups in that report (Dickey et al., 2002a,b). In the current report the more posterior transverse gyri may not have been included. Fifth, there is marked inter-subject and even inter-hemispheric variability of the STG, particularly, Heschl's gyrus (Lange et al., 1997; Leonard et al., 1998; Sweet et al., 2005; Knaus et al., 2006). To clarify, it is quite common for there to be two parallel transverse or Heschl's gyri (Knaus et al., 2006; Sweet et al., 2005). However, these parallel transverse gyri can be completely separate or partially separate. If they are partially separate they can be merged medially, part way down the gyrus, or laterally. What should one consider as Heschl's gyrus is not clear. Should one include both, part of both, or only the more anterior one? Both the prior report and this paper used Steinmetz's criteria (Steinmetz et al., 1986) as the posterior boundary. This arbitrary criteria state that if the gyri are merged medially with a common stem, then one can include both. If they are merged part way down the gyrus or laterally, then they should be divided into two separate gyri and only include the more anterior gyri as Heschl's. Note that this criteria is helpful, but arbitrary. Subtle differences in visualization abilities or in morphometry can result in significant volume differences which may not be meaningful functionally. Indeed, the functional anatomy of AI (primary auditory cortex) may not be restricted to medial Heschl's gyrus, regardless of its definition or criteria (Sweet et al., 2005). Indeed, recent work suggests that there may be two primary auditory receptive fields in the human auditory system, one more medial, one more lateral (Engelien et al., 2002). Close inspection of the receptive field maps (Engelien et al., 2002) suggests that the more lateral field may be partially located on what may be considered by Steinmetz's criteria to be the second transverse gyrus, an area more likely captured in our first report but less likely captured in this current report. That functionally important area (Sweet et al., 2005) may represent the difference in these two reports. Indeed, other workers suggest that volume asymmetries in the region of the primary auditory cortex do not correspond to functional activation while hearing

tones and word pairs (Yoo et al., 2005), possibly due to the poor matching of gyral sulcal patterns and cytoarchitechtonically defined acoustic regions (Morosan et al., 2001), and marked variation in the morphology of Heschl's gyrus (Leonard et al., 1998) (Sweet et al., 2005). Furthermore, regional differences in STG volumes are more marked in schizophrenia than in controls (Park et al., 2004). In sum, the lack of replication of our previous report is likely due to a combination of factors: differences in subject demographics, presence of co-morbid disorders, subject N, difference in measurement tools, and intersubject morphometric variability of Heschl's gyrus particularly in the schizophrenia spectrum.

Despite these limitations to direct comparison between the two samples, the lack of difference between groups in Heschl's volume in this study is informative: one cannot attribute differences in activation in the current report to subtle volume differences of Heschl's gyrus per se. There may be subtle differences in volumes in the adjacent cortical regions, perhaps in areas 41 and 42 or the larger STG not measured by the current report. However, even if there were smaller volumes in the adjacent cortex in SPD subjects, one would not have predicted that smaller volumes lead to larger areas of activation, more likely, smaller volumes would predict smaller areas of activation. Therefore, we do not believe that possible volume differences in peri-Heschl's regions can account for the between group differences in activation patterns.

The possible relationship between abnormal auditory sensory processing and clinical measures was also investigated. Exploratory correlations between ROI and clinical/cognitive symptoms suggest that these early auditory sensory processing problems may have implications for downstream language functioning. Specifically, in SPD subjects, there was a correlation between abnormal activation on the right during the pitch experiment with odd speech. Odd speech and formal thought disorder likely represent a symptom continuum. Our laboratory previously demonstrated thought disorder correlating with left STG volumes in female SPD subjects (Dickey et al., 2003). Similarly, in schizophrenic subjects, correlations have been shown between thought disorder and hallucinations with bilateral measures of volume and function of temporal lobe regions (Shenton et al., 1992; Dierks et al., 1999; Kircher et al., 2001; Barta et al., 1990; Woodruff et al., 1997). In this report, however, the correlation with odd speech occurred with right-sided activation. Odd speech in SPD may be characterized by impoverished prosody (Dickey et al., unpublished data). Consensus suggests a right hemisphere advantage for emotional (non-semantic) aspects of language and prosody (Mitchell and Crow, 2005), particularly in the right STS and MTG, whereas more semantic aspects of language recruit more left-sided regions (Mitchell et al., 2003). This hemispheric pattern has been seen using fMRI (Mitchell et al., 2003) (Wildgruber et al., 2005), transcranial Doppler ultrasonography (Vingerhoets et al., 2003), repetitive transcranial magnetic stimulation (van Rijin et al., 2005), event-related potential (Eckstein and Friederici,

2005), and in lesion studies (Pell, 2006). Therefore, it is possible, that the tone processing impairment on the right in the SPD subjects is related to non-semantic aspects of their odd speech.

Other aspects of language, specifically verbal learning, also correlated with inappropriate activation of right-sided ROI for the current pitch experiment. Again, this is similar to findings in schizophrenia. Using PET, Ragland et al. demonstrated impaired verbal learning correlating with STG activation abnormalities (Ragland et al., 2001).

There are several limitations to the current study. One limitation is the large number of correlations performed as discussed in the Methods section. However, including these exploratory findings in this paper may serve to generate future hypotheses about the relationship between auditory processing and clinical features in this understudied schizophrenia spectrum disorder. Second, only male subjects were included in this study. Future work will need to include females to test whether there is a gender effect (Dickey et al., 2003; Knaus et al., 2006). This is particularly critical as our laboratory recently completed a pitch MMN investigation in a group of male and female SPD individuals and the results suggest that there is no impairment of early sensory processing as indexed by MMN in males. Instead, the significant pitch MMN reduction was found in females (Niznikiewicz et al., in submission). Third, the whole sample size is small relative to fMRI studies in schizophrenia. This reflects the inherent difficulty in recruiting SPD subjects who are not part of a clinical population for a research study. Had we had access to a larger group of SPD subjects then the findings could be more generalized to all SPD subjects. Nonetheless, these data suggest that for at least a subpopulation of SPD subjects, there may be deficits in early sensory processing of tones. Fourth, there was a difference between groups in terms of education. However, we are not aware of any paper suggesting that education plays a role in simple tone processing per se. Fifth, shifting gradients in the MRI scanner are loud and theoretically may have caused more sensory interference for SPD subjects than for control subjects. Although all subjects used earphones, one cannot rule out systematic affect of scanner noise. We note that a silent event-related design, in which the scanner would not scan during stimuli presentation, would more fully remove the confound of interference from scanner noise. Unfortunately, such a design would also significantly increase the scanning time (a mean of 14 s between stimuli as proposed by Amaro et al., 2002. In addition, one cannot modulate scanner frequency or pitch, thus limiting the exploration of differential pitch discrimination in SPD subjects. Sixth, there is no behavioral output measure during the experiments. This limits the ability to determine what the subject is doing while hearing the tones and, therefore, limits the ability to draw firm interpretations of the results.

That is, one cannot definitively conclude that the SPD subjects exhibit inefficient processing *vs* exaggerated responses to deviant tones. However, one can state that

it appears that SPD subjects recruit more neurons while hearing simple tones than comparison subjects. Having a behavioral response, however, would have added a layer of complexity by introducing other potential confounds such as SPD subjects' ability to make decisions, processing speed, and motor speed. Finally, one limitation common to the fMRI literature is that data were collected for each subject on only one time point. Recent work has shown marked intersession variability for the extent of activation emanating from listening to tones or word pairs (Yoo et al., 2005).

Nonetheless, these data suggest that neurolepticnaïve SPD subjects, compared with matched comparison subjects, demonstrate inefficient or hyper-responsive early processing of pure tones. This atypical processing may be correlated with some of the core features of SPD, namely, odd speech and impairment in verbal learning.

Contributors   *Dickey*: designed the study, collected the fMRI data, analyzed the clinical and fMRI data, and wrote the manuscript. *Morocz*: analyzed the fMRI data. *Niznikiewicz*: collected and analyzed the ERP data, and contributed to the manuscript. *Voglmaier*: collected and analyzed CVLT data, and performed SCID interview. *Dreusicke*: analyzed the fMRI data. *Toner*: aided in fMRI data collection. *Yoo*: aided in initial fMRI data collection. *Khan*: aided in final fMRI data presentation. *Shenton*: reviewed the manuscript. *McCarley*: reviewed the manuscript.

Conflict of interest   All authors declare that they have no conflict of interest.

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Discussion

Mental processes

Mental processes are short–lived phenomena in the range of tens or hundreds of milliseconds[4]. Common tomographic imaging methods do injustice to time by neglecting the brain's temporal agility[10,56] at the neurovascular level[41,50] with deleterious consequences: Interpretations based on current acquisition and analysis methods consider necessarily very few time points in an arguably rich neural recruitment tree. Activation blobs resulting from interpolation and averaging at best represent one or two stations in the functional cascade associated with a mental trigger. Subsequent inferences, blinded by such a large but epiphenomenal effect, may be oversimplified and omit the underlying source of a neurological condition.
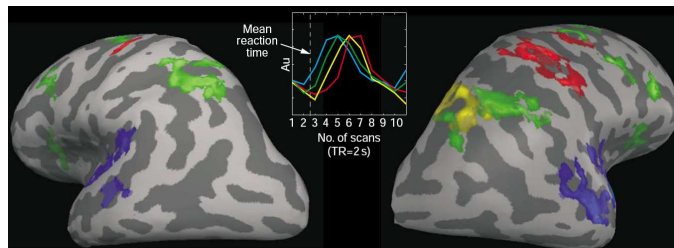
Fig. 6 Example of a complex and _serial_ task using fMRI in mental chronometry during a visuo-spatial mental imagery. Analysis is based on ICA. Different colors therefore represent different ICA components: (blue) for auditory and language regions, (green) mainly left PPC, (yellow) right PPC in IPS, (red) sensori-motor regions. [13]
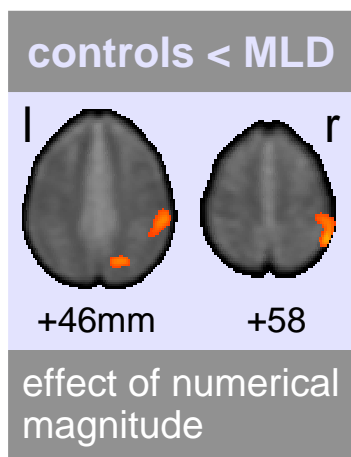
Fig. 7 Comparison of the parametric effect of _numerical magnitude_ in healthy subjects and subjects suffering from developmental dyscalculia. The HRF based analysis reveals mainly one confluent large single hot spot in the **right intraparietal sulcus** that undergoes in DC a stronger signal change associated with the parametric numerical multiplication product size as compared to control.

For example, the true problem for many subjects with MLD (Mathematical Learning Disability, Fig. 7) may not reside in the **right intraparietal sulcus**[9] but instead seconds earlier in the activation cascade, perhaps in the **right cerebellum** (see Fig. 10), where healthy neural networks may contribute as hyperfast assessors of numerical magnitudes for the successful solving of a mental multiplication task[36,38].

In order to compute cognitive roadmaps of neural recruitment the temporal sampling rate needs to be satisfactorily high during data acquisition. The desired effects, _i.e._, BOLD signal changes, are primarily metabolic equivalents of oscillatory waves called 'gamma bursts', essentially an electrical phenomena that resonate at a frequency of around 40 Hz and last for about 50 to 5000 ms[5,12,30,56]. They appear to directly result from large neuronal cell assemblies working in unison[43,56], and are associated with thinking and are in this respect indicators of cognition at work[4,41]. Importantly,

the hemodynamic response turns out to be much less sluggish than long assumed (see page 1 and Figs. 1–3): capillaries and arterioles change their vessel bed diameter within 50-100 ms following neuronal activity in their neighbourhood[29,30,44,54].

An ideal stimulus vector

The technical advancements of the last few years raise hope that some limitations in the fMRI techniques relevant dur-

Fig. 8 Evidence is shown that local field potentials are plausible to characterize high frequency perisynaptic spiking activity (c) which correlates best with the observed BOLD signal time course.[29]

ing data acquisition will be solved. For example the difference in the timing of individual 2D slices acquired as a 3D stack is a serious hindrance for accurately determining the order of activation foci (page 3). A hierarchic map of active brain areas based on such fMRI data, recruited task–free over time or during a specific task, cannot be computed orderly if such is the goal in a given experiment. Complex tasks summon inherently numerous brain regions where the measured activation signal is ideally associable with the initial stimulus and the subsequent mental processes. New super-fast single-shot techniques[22,28,45] are a necessity for investigating the internal schedule within activation trees where foci are likely distributed over time and throughout the entire brain. Ultimately the main motivation for using high–speed BOLD imaging techniques is the desire to parcel cognitive tasks at the highest possible temporal resolution in order to draw accurately inferences about the numerous functional substations involved.

I found that *arabic numerals* and *numerical calculation* are plausible vehicles that elicit brain responses in a *parametric* and controllable fashion. Numbers serve as convenient vectors that metabolically drive neural structures by exposing them to magnitudes and ratios intrinsic to the numerical stimuli and arithmetic operations. Furthermore, numerical values remain *traceable* throughout a mental calculation task via their parametric exertion on neural response. Cognitive units of the psychophysical processing stream for numbers and arithmetic modulate neural involvement and by doing so act as logical signatures in the resulting *cascade* of highly specific metabolic brain responses to calculation. Figure 9 gives an indication of the complexity of spatial and temporal evolution at a subset of the distinct activation foci in an fMRI test described below.
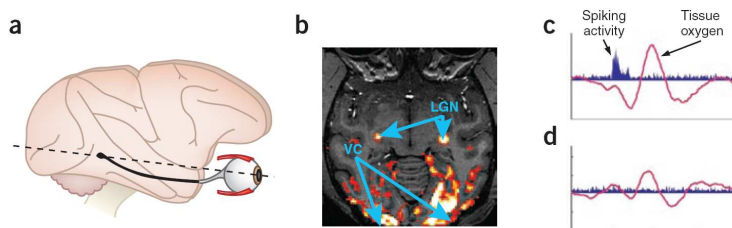
Three different analysis methods

I completed a series of both functional and high–resolution anatomical MRI scans on a population with developmental dyscalculia and a control population of adults in a collaborative study with Dr. Ruth Shalev at Jerusalem Shaare Zedek Medical Center in Israel. It revealed regions in normal subjects that we believe are implicated in arithmetic calculations. The subjects performed an arithmetic task lasting more than four seconds, in which they had to multiply two numbers, decide on the *in*correctness of the offered result, and respond by pressing one of three buttons. Voxel based morphometry (VBM) revealed a distinct gray matter enlargement in subjects with dyscalculia in both intraparietal sulci, a deep fissure in

Fig. 9: Hierarchic cascade of brain activations during mental multiplication and estimation in healthy controls. The white diagonal depicts temporal drift over time of phase for one arithmetic event, where top reflects the event's beginning, and bottom the event's end. Colors of boxes with white digits correspond in time with colors of spheres in the glass brains at figure top.

both upper parietal lobes, though more in the right hemisphere, a feature that was also observed in subjects with Turner syndrome[35], or with low birth weight[24] in the left hemisphere. Importantly, the anatomical location of these cortical abnormalities corresponded with the activation differences detected by fMRI described below. The use of a 3D PRESTO BOLD sequence[46,55] for the fMRI study allowed us to trace down for the normal control population a neural system involved in mental arithmetic. For this I developed a technique for event–related (*time–locked*) signal averaging that depicts the temporal evolution of the MR signal in brain areas involved in this complex tasks (Fig. 9). The approach allows us to reveal in the task–specific neural maps visually a meticulous segregation in time and a delineation in space, which ultimately will permit to systematically explore the functional differences between dyscalculic and unaffected controls on a fine–grained ground. Mental arithmetic appears to be carried out by a wealth of brain areas tightly orchestrated in a hierarchic fashion. Selected brain regions that are sequentially activated in the healthy population during the mental multiplica-

tion and estimation task are depicted in glass diagrams in the upper part of the figure.
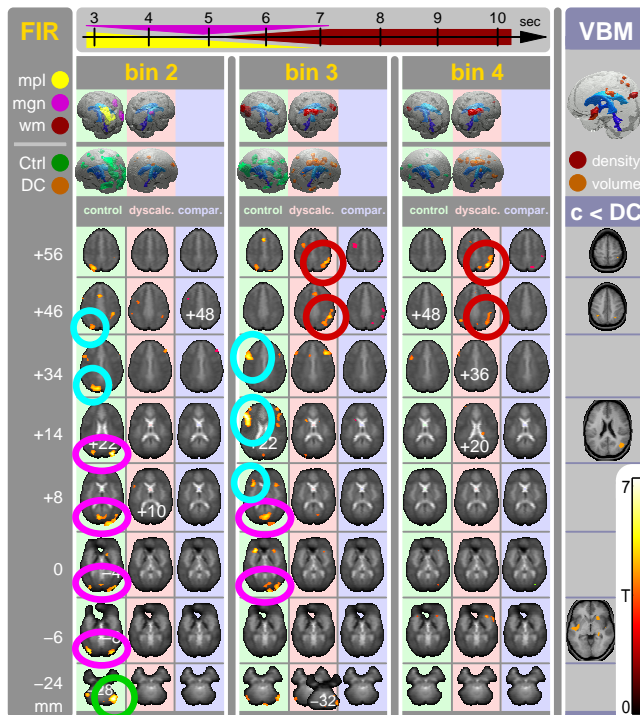
Fig. 10: Awareness for number size during mental multiplication and estimation. *Green* circle: **Early** cerebellar response in controls. *Pink* and *Turquoise*: Visual cortex and language areas in controls, respectively; *Red*: **Delayed** activation in right intraparietal sulcus. Apparent is the highly aberrant response to number size in developmental dyscalculia.

In contrast, the results of a FIR analysis using proper statistics in the GLM framework with the very same data set is shown in figure 10. This method allows us to delimit the resulting activation patterns into separate time bins. Here too, our data suggest that in normal subjects the **right cerebellum** is involved *early* in magnitude assessment (green circle in Fig. 10; area six in Fig. 9) while the same region is hardly active in dyscalculic subjects. Such observations about aberrant pathways help delineating the core problem of DC, which perhaps commences in a dysfunctional cerebellum. Because the memorization of rote multiplication tables requires the correct assessment of number size[6], subjects with DC may therefore benefit from therapeutic interventions that emphasize the strengthening of magnitude–processing skills.

Furthermore, the entire dyscalculic brain appears to be less responsive to the numerical magnitudes of the numbers processed at the *later* stages in the calculation hierarchy. The major exception to this general impression of an overall lowered activation level in the dyscalculic brain during numerical computation resides in the **right intraparietal sulcus** (Fig. 7; and *red* circles in Fig. 10). This area in dyscalculic subjects presents with an abnormally delayed but enhanced metabolic response to numerical magnitude, which perhaps reflects the moment when the results of the multiplication operation are stored in short–term working memory for the subsequent the numerical estimation process. This is exactly the spot where we also detected abnormal gray matter accumulations in the anatomical studies. This finding implies that dyscalculic subjects use *different* mental strategies for numerical calculations than control subjects.

An unexpected result in our first fMRI study on dyscalculia was the remarkably distinct, number–size related modulation of the **occipital areas** in control subjects. It is strongly suggestive for a functional coupling of processing numerical magnitudes within large parts of the visual processing stream (*pink* circles in Fig. 10), in contrast to the near–complete absence of such modulation in subjects with dyscalculia. This activation in the visual stream during magnitude estimation suggests that functional connections were established during development between both numerosity and magnitude encoding regions and many other brain areas that process sensory inputs. This idea is consistent with the common experience of a visual conception of intermediate arithmetic results and the corresponding digits, or a subvocal utterance and the subsequent 'hearing' thereof (see *cyan* circles left frontal in Fig. 10).

Final notions

I showed that common fMRI studies, as designed nowadays, successfully reveal commonalities and differences within and between subject groups. But due to the tardiness of the way data is acquired, and the way analysis algorithms are adapted to the slowness intrinsic to the data, only a few principle regions with distinct signal are recognized when using traditional methods. Importantly, the information about the temporal cascade of neural recruitment may be *hidden* entirely and consequently neglected simply.

I am going to list here shortly a few ideas I encountered through my exposure to works of my own and of my current collaborators I share projects with which deem to me as potential ways out of the dilemma outlined above: • application of high–speed, single–shot, parallel-imaging, full–brain acquisition techniques for BOLD fMRI[23,28,55] • development of radically novel time-course sensitive analysis methods that address latency, functional connectivity[36] and connectedness among salient regions • invention of novel mathematical models that analyze and describe the functioning of neural circuitry of complex cognitive tasks in an abstract where time and space lose their customary meaning • use of intelligent paradigms that account realistically for neurophysiological mechanisms and their limitations and reflect this in paradigm designs properly adapted to the cognitive tasks in question • use of paradigm designs that respect a simple law, true for any type of data measurement, which is to take into consideration a high ratio of

data sampling frequency *versus* the frequency expected from neural responses described by the BOLD phenomenon[14,36,38,39]. I foresee the realization of such methodological advances in numerous technical details, as I outlined in my 'wish-list' before - which *per se* are 'no more' than sophisticated individual links within a long chain of techniques - as a highly advantageous undertaking, if substantiated, for the fMRI processing stream as a whole. While the such meliorated sub–methods may well play a role in their own scientific framework, only *unison*, in concert with the other methods, will they lead to a überproportionate breakthrough and to the quantum leap needed for efficient cognitive brain mapping.

In summary, I covered in this last paragraph three aspects of technical progresses in areas such as image acquisition, image processing and design of experimental paradigms, which I regard as essential key advances for a successful tracing of activity inside neural networks by fMRI. These and similar future strategies shall in my opinion open windows of opportunities for new hypotheses *i)* about the temporal *orchestration* of active brain areas involved in human thinking and *ii)* about the electrophysiological *networks* that transiently interconnect such areas.

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