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The Potential for New Understandings of Normal and Abnormal Cognition by Integration of Neuroimaging and Behavioral Data: Not an Exercise in Carrying Coals to Newcastle

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Abstract Discovering the means to prevent and cure schizophrenia is a vision that motivates many scientists. But in order to achieve this goal, we need to understand its neurobiological basis. The emergent metadiscipline of cognitive neuroscience fields an impressive array of tools that can be marshaled towards achieving this goal, including powerful new methods of imaging the brain (both structural and functional) as well as assessments of perceptual and cognitive capacities based on psychophysical procedures, experimental tasks and models developed by cognitive science. We believe that the integration of data from this array of tools offers the greatest possibilities and potential for advancing understanding of the neural basis of not only normal cognition but also the cognitive impairments that are fundamental to schizophrenia. Since sufficient expertise in the application of these tools and methods rarely reside in a single individual, or even a single laboratory, collaboration is a key element in this endeavor. Here, we review some of the products of our integrative efforts in collaboration with our colleagues on the East Coast of Australia and Pacific Rim. This research focuses on the neural basis of executive function deficits and impairments in early auditory processing in patients using various combinations of performance indices (from perceptual and cognitive paradigms), ERPs, fMRI and sMRI. In each case, integration of two or more sources of information provides more information than any one source alone by revealing new insights into structure-function relationships. Furthermore, the addition of other imaging methodologies (such as DTI) and approaches (such as computational models of cognition) offers new horizons

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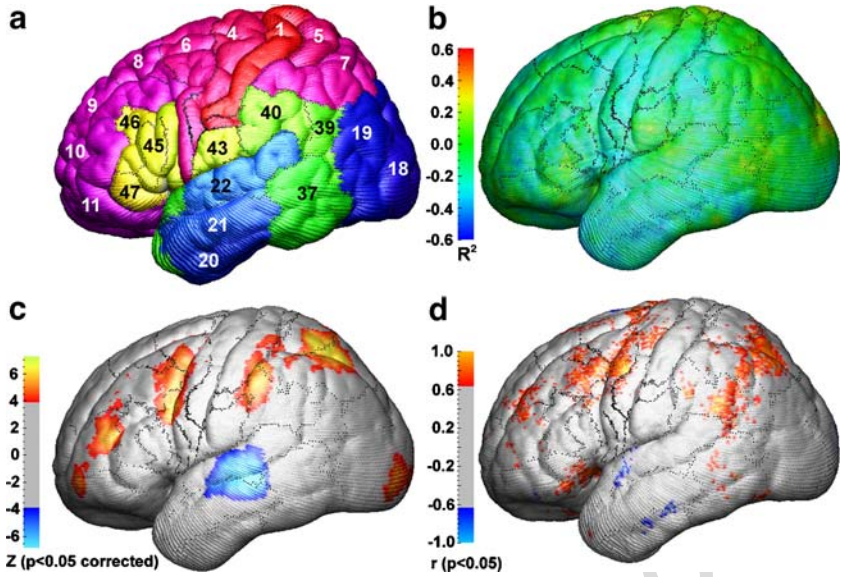

Fig. 1 **a** Deformable Brodmann area atlas that is warped into the probabilistic model of the brain surface (left hemisphere). **b** Statistical maps (ANOVA) of cerebral cortical gyral pattern averaging with task by group (10 male right-handed first-episode schizophrenia patients *vs* 10 matched healthy control subjects). Scale: R^2=−0.60 (blue) for reduced and R^2=0.60 (red) for increased grey matter in schizophrenia. **c** Statistical maps for the combined group (N=20) BOLD response as a function of task difficulty when performing the Tower of London task showing increased activation in the prefrontal, frontal and parietal cortex and a negative BOLD response in the superior and middle temporal gyri. *RESEL*–corrected statistical thresholds at P<0.05: Z< −3.88 for negative BOLD (blue) and Z>3.88 for positive BOLD (red). **d** Statistical Pearson correlation maps of cerebral cortical grey matter thickness by BOLD response suggest reduced BOLD response with decreased cortical grey matter thickness in the prefrontal, frontal and parietal cortex due to reduced grey matter in first-episode schizophrenia patients (N=10). Uncorrected statistical thresholds: r<−0.63 (blue) and r>0.63 (red). Modified from Rasser et al. (2005)

in human brain imaging research and in understanding human behavior.

Keywords Schizophrenia · Auditory processing · Executive functions · Event-related potentials (ERPs) · Mismatch negativity (MMN) · Functional magnetic resonance (fMRI) · Structural magnetic resonance imaging (sMRI)

Introduction

The focus of neuroimaging research at Newcastle (-upon-Hunter) which like its namesake (Newcastle-upon-Tyne) is famous[1] for its coal exports, has for the last decade or so been focussed on understanding the nature of the brain disorder that is schizophrenia. Schizophrenia is a devastating mental illness affecting approximately 1% of the population. The diagnosis of schizophrenia is criterion-based and reflects clinical consensus important for patient management that may have little relevance to underlying neurobiology. In contrast to earlier characterizations of the disorder which focused on clinical signs and symptoms, cognitive deficits have become increasingly accepted as a remarkably robust characteristic of the disorder with numerous quantitative meta-analyses producing substantial effect-size estimates of differences between schizophrenia patients and healthy controls.

Besides marked deficits in verbal declarative memory, general intellectual ability, and attention (Heinrichs 2005), all of which produce effect sizes of 1.00 or more, two other areas exhibiting substantial effect sizes are cognitive tests assessing executive functions (Heinrichs 2005) and electrophysiological indices of early auditory information processing (Umbricht and Krljes 2005). We have focused on these two areas in a research program that utilizes and integrates information from a range of methodologies – psychophysical and behavioral measures of performance, structural or functional neuroimaging methods including sMRI, fMRI and ERPs – to elucidate the disturbances in brain structure-function relationships that underpin these core impairments in schizophrenia.

Our integrative endeavors at Newcastle while in their infancy and having benefited from collaborations with our Pacific Rim colleagues, are already yielding new insights into function-structure relationships in unaffected healthy individuals as well as in patients. A key resource in our integrative efforts is that Newcastle is the host site for the Schizophrenia Research Institute's Virtual Brain Bank (VBB) - a comprehensive multimodal database containing high-resolution structural and functional MRI data, clinical

[1] Or infamous depending upon your views on the role of emissions from coal fired power generators on climate change!

and neuropsychological data, and genetic information (e.g., DNA and RNA gene expression data). It currently contains data from around 250 people diagnosed with schizophrenia at various stages of their disease, cannabis users (with and without psychosis) and healthy volunteers. In coming years, this database will grow to a target of 4,000 individuals (2,000 patients and controls) as part of the recently established Australian Schizophrenia Research Bank (ASRB), a multi-centre collaborative project across four east coast sites (Newcastle, Brisbane, Sydney, Melbourne) and Perth on the west coast. The ASRB will eventually provide Pacific Rim and international researchers with access to comprehensive linked data in the clinical, cognitive, genetic, and brain imaging domains thus enabling researchers to address important questions that require large sample sizes.

Executive functions

Data housed by the VBB were utilized in a novel approach to assess structure-function relationships in a group of first-episode schizophrenia patients when performing the Tower of London (TOL) task, an executive function task that tests planning ability (Rasser et al. 2005). The major challenge in analyzing grouped brain MRI data of this type derives from aligning the unique structural features of each individual brain. This is particularly so for patients who may exhibit decreased spatial overlap of cortical regions compared to control subjects.

To reduce potential confounds, the VBB applies a cortical pattern matching method developed at the Laboratory of Neuro Imaging (LONI) at the University of California Los Angeles (Thompson et al. 2004). Cortical pattern matching involves the explicit definition of individual cortical features and uses these for the accurate alignment of gyral structures across all subjects. Local extensions of this technique have included applications to the cerebellum and algorithms that allow automatic referencing with standard brain atlases (i.e. Deformable Brodmann's area atlas; Fig. 1a).

In the first study of its kind, cortical pattern matching techniques were used to integrate structural and functional measures in the assessment of cortical regions and TOL

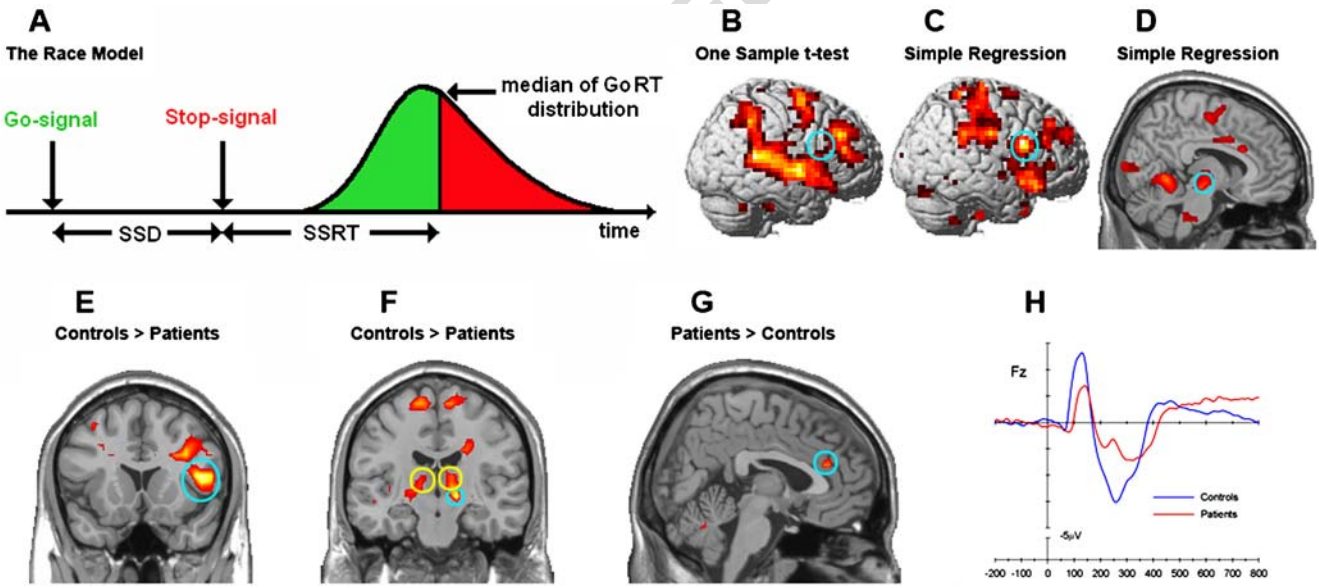

Fig. 2 *Top panel.* **a** Estimation of SSRT: The speed of stop processes, the *stop-signal reaction time (SSRT),* is estimated by modeling stop-signal performance as a race between two independent processes: the response activation (*go*) process and response inhibition (*stop*) process. The proportion of stop trials that are successfully inhibited under the curve depicting the distribution of go RTs. (PI; red portion) represents trials where the stop process is fast enough to beat the go process. For the remaining proportion, the go response process escapes inhibition (PR; green portion). The point in the RT distribution where this 'cut-off' between PI and PR occurs is used to estimate the speed of stop processes for an individual: SSRT = $RT_{cut\text{-}off}$ minus SSD. B-D illustrate different models of BOLD prediction focusing on rIFG and rSTN activation (circled in blue) **b** Stop related activity based on a one-sample t-test revealing minimal rIFG activation in BA44; (C-D) Simple regression using SSRT to predict BOLD responses in the same contrast maps used in B revealing rIFG **c** and rSTN **d** activation. Cohen's d and Pearson's r calculated for peak voxels (MNI cords) in rIFG (52 16 20; r=0.81, d=2.52) and rSTN (8 - 16 -8; r=.78, d=2.75). (Hughes, Michie, Fulham and Badcock, in preparation) *Bottom panel.* **e** Controls exhibited greater BOLD activation than patients within rIFG (blue circle), **f** rSTN (blue circle) and bilateral thalami (circled in yellow to distinguish from rSTN); **g** Patients exhibited greater activation within ACC (blue circle) than controls. In B-G, all display thresholds were p<.05, and 10 contiguous voxels; yellow indicates higher t-score than red. **h** Patients generated smaller and later N1 and P3a components than controls at Fz in ERPs to stop tones on successfully stopped trials and also produced an N2 component that was not seen in control ERPs. (Hughes, Michie, Smith, Fulham, Badcock, in preparation)

problem solving performance (Rasser et al. 2005). We reported a correlation between reduced grey matter thickness (based on gyral pattern averaging-derived measures of cerebral grey matter thickness: Fig. 1b) and blood oxygenation level-dependent (BOLD) activation when performing the TOL task in right-handed male first-episode schizophrenia patients (Fig. 1d). Reduced task difficulty-dependent activation as a function of reduced cortical grey matter thickness was predominantly found in the left prefrontal, right orbitofrontal, right superior temporal as well as left and right parietal cortex (Fig. 1c). This novel finding suggests that a reduction of regional grey matter in first-episode schizophrenia patients is associated with impaired executive brain function.

Other current research on executive functions is focussed on two paradigms developed by cognitive scientists that target subcomponents of executive control, the stop-signal and task-switching paradigms, respectively. The former assesses the capacity for response inhibition by presenting a stop-signal, usually a tone, after a binary choice visual go signal and provides an estimate of the speed of inhibitory processes, the stop-signal reaction time (SSRT - Fig. 2a). SSRT is the main dependent variable derived from stop-signal paradigms. Normally, the timing of the stop-signal relative to the go signal, the stop-signal delay (SSD), controls the difficulty of inhibition-longer SSDs are linked to more difficult inhibition because Go response preparedness has progressed to a later stage. Previous research (Aron and Poldrack 2006) has linked stop-signal inhibition to activation in right inferior frontal gyrus (rIFG; BA44) and subthalamic nucleus (rSTN). In our current research, we used a variant of the stop-signal paradigm where stop-signals were set relative to mean Go RT, affording each participant (N=14) equal time to effect response inhibition. Therefore, the difficulty of control was determined by an individual's SSRT: slower SSRT required response inhibition

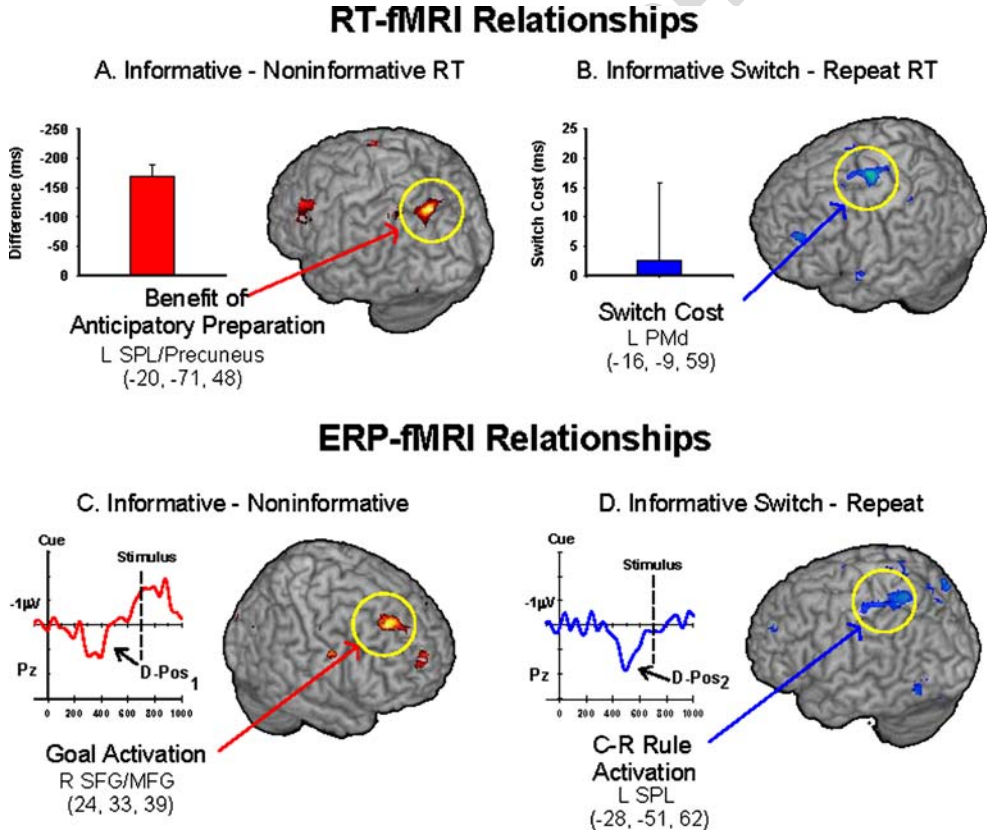

Fig. 3 *Top panel*: Relationship between behavioral RT measures and fMRI activation. **a** Relationship between the benefit of anticipatory preparation (reduction in RT for informative trials relative to non-informative trials) and informative - noninformative BOLD contrast; **b** Relationship between informative switch cost (difference in RT for informative switch relative to informative repeat trials) and informative switch – informative repeat BOLD contrast. *Bottom panel*: Relationship between ERP measures and fMRI activation. **c** Relationship between D-Pos$_1$ (cue-locked informative minus noninformative difference waveform at Pz electrode) and informative–noninformative BOLD contrast. **d** Relationship between D-Pos$_2$ (cue-locked informative switch minus informative repeat difference waveform at Pz) and informative switch –informative repeat BOLD contrast. *Both panels:* Positive correlations between the behavioural, ERP, and the BOLD contrasts determined using multiple regression - contrasts thresholded at P<.001, with a minimum cluster size of 5 voxels; only regions significant at P<.05 cluster level shown (N=15). Abbreviations: L, left; R, right; SPL, superior parietal lobule; PMd, dorsal premotor cortex; SFG, superior frontal gyrus; MFG, middle frontal gyrus; DLPFC, dorsolateral prefrontal cortex; S-R, stimulus-response; C-R, category-response. (Jamadar, Karayanidis, Hughes, Fulham & Michie, in preparation)

to be effected at a later stage of Go response preparedness. SSRT (range=136–275 ms) was directly related to the probability of response inhibition across participants. When a one sample t-test was performed comparing correct Stop trials to correct Go trials (Fig. 2b), rIFG was observed in BA 9/46, but activation in BA44 was minimal, and rSTN not significant. Simple regression analyses of these contrast images and SSRT revealed significant BOLD correlated variance in posterior rIFG (Fig. 2c; BA44), rSTN (Fig. 2d) and the thalamus (not shown), indicating that subjects with longer SSRTs showed greater rIFG/rSTN activation demonstrating the usefulness of integrating behavioural and BOLD measures that are concurrently recorded.

As our previous research has provided evidence of inhibition deficits in schizophrenia patients (Badcock et al. 2002), we have recently recorded fMRI and ERP data from patients with schizophrenia and controls (N=10 for each group) matched for age, sex, and years of education, performing a stop-signal paradigm where inhibition success was equal (50%) for all participants. BOLD contrasts showed that controls exhibited greater rIFG (Fig. 2e; BA44) and rSTN and bilateral thalami (Fig. 2f) than patients, whereas patients exhibited greater activation within limbic cortex (see Fig. 2g; ACC) suggesting that patients were using at least a partially different network to controls for effecting response inhibition. ERPs however showed that not only were the N1 and P3a components to the stop signal tones smaller in patients than in controls, these components were also delayed in peak latency (Fig. 2h). In addition, patients exhibited an N2 component not evident in controls. Since previous research has linked N2 to monitoring of response conflict and to generators in ACC, convergent information derived from fMRI and ERP data suggest that the overall slower processing of stop signals by patients results in greater response conflict between two possible behavioral outcomes-response execution vs. response inhibition.

In cued trials task-switching paradigms, participants alternate between two tasks using information provided by a cue presented prior to each trial. RT is longer for switch compared to repeat trials and this switch cost decreases with increasing cue-stimulus interval (CSI), an effect attributed to an anticipatory task reconfiguration process. We have shown that this preparatory process is indexed in cue elicited ERPs by an increase in posterior positivity in anticipation of a switch relative to a repeat trial – the differential switch positivity (D-Pos; Karayanidis et al. 2003).

In our current research, we combined design manipulations and multiple imaging modalities to gain insights into the brain networks involved in task reconfiguration in healthy participants in a cued trials paradigm with both informative cues (valid cuing of upcoming task) and non-informative cues (cue timing but not task identity). ERP results indicated at least two processes associated with anticipatory preparation: D-Pos$_1$ differentiated between informative and non-informative cues, whereas D-Pos$_2$ differentiated between informative switch and repeat cues. We propose (i) that anticipatory preparation includes two constituent processes: goal-activation and category-response (C-R) rule activation and (ii) that these processes can be mapped to D-Pos$_1$ and D-Pos$_2$, respectively, propositions that are supported by analyses of the relationship of behavioral and D-Pos indices of these two processes with BOLD activation (see Fig. 3). The benefit of advance preparation (RT non-informative–informative cues) was positively correlated with activity in the left superior parietal lobule (SPL)/precuneus (Fig. 3a), a region implicated in 'holding' task-

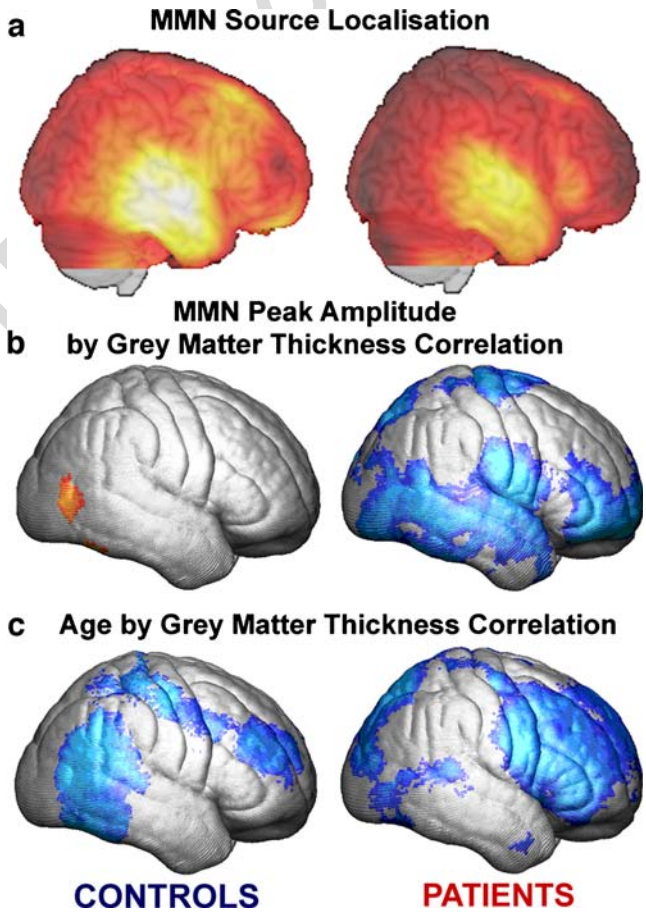

Fig. 4 **a** Current source densities of mismatch negativity (MMN) co-registered on individual high-resolution MRI scans and transformed into MNI space for group analysis derived from LORETA constrained source localisation performed on current dipoles, oriented perpendicular to cortical surface in realistic head models (CURRY). **b** Correlation of cortical grey matter thickness with Fz-recorded MMN peak amplitudes (P<0.05) to frequency deviants using cortical pattern matching. **c** Note that correlation of reduced MMN with reduced grey matter thickness (P<0.05) in schizophrenia in MMN source areas of the right temporal lobe are not explained by normal ageing effects on grey matter thickness **c** (Rasser, Todd, Thompson, Michie, Ward, Johnston, Case, Tooney, Schall, in preparation)

relevant S-R rules. Switch cost on informative (prepared) trials was associated with activity in the dorsal premotor cortex (PMd; Fig. 3b), a region associated with planning motor actions for goal-directed behaviour. D-Pos$_1$ amplitude was associated with activity in the DLPFC (superior and middle frontal gyri SFG/MFG: Fig. 3c), a region implicated as the locus of a top-down biasing signal to guide behaviour whereas D-Pos$_2$ amplitude was associated with activity in the SPL (Fig. 3d). These results are consistent with multi-component models of anticipatory preparation and suggest that distinct neural areas underlie goal activation and C-R activation. We are currently utilising a similar combination of behavioral, ERP and fMRI data to understand the neural basis of reduced anticipatory D-Pos in patients (Karayanidis et al. 2006).

Early auditory processing

One of the most consistent research findings in schizophrenia is a reduction in the amplitude of an early auditory event-related brain potential, known as mismatch negativity, or MMN (Umbricht and Krljes 2005). MMN occurs whenever the auditory system detects a change, a deviant sound, against a repetitive background of stimulation. The process is largely automatic and does not require active attention. A substantial body of research (Näätänen et al. 2001) indicates that MMN generation is underpinned by a sensory memory system that enables the brain to process sounds with respect to a relevant acoustic context and to automatically identify those deviant events that might be significant prompting an attention switch for further processing. MMN is maximal at midline frontal sites (Fz) and reverses in polarity at the mastoids (using a nose reference). MMN has multiple anatomical generators in the supratemporal plane of auditory cortex and some evidence of additional contributions from a right frontal generator (Näätänen et al. 2001)

Over the past two decades, we have conducted numerous investigations into how MMN reduction in schizophrenia depends on characteristics of the deviant stimulus (duration, frequency, and intensity); age; duration of illness (Todd et al. 2008); modulation by attention; and medication. We have used a range of modalities in addition to the standard EEG recording of MMN, such as functional MRI (Schall et al. 2003), Positron Emission Tomography and current source density measures.

Using a multimodal approach facilitated by the VBB, we have recently extracted preliminary data confirming an association of smaller MMN amplitudes in schizophrenia to frequency deviants with grey matter thickness reduction in cortical areas subserving auditory processing (Fig. 4b). The topographic distribution of MMN and grey matter associations in patients is consistent with our source localisation data that implicate temporal cortical areas in the generation of MMN in both controls and patients (Fig. 4a). The lack of MMN amplitude by grey matter correlations in healthy controls (Fig. 4b) suggests that MMN amplitude reduction in schizophrenia is associated with brain pathology, rather than with normal age variability-related changes (Fig. 4c).

However, reviews of the MMN literature suggest that the impairment in auditory processing in schizophrenia may be

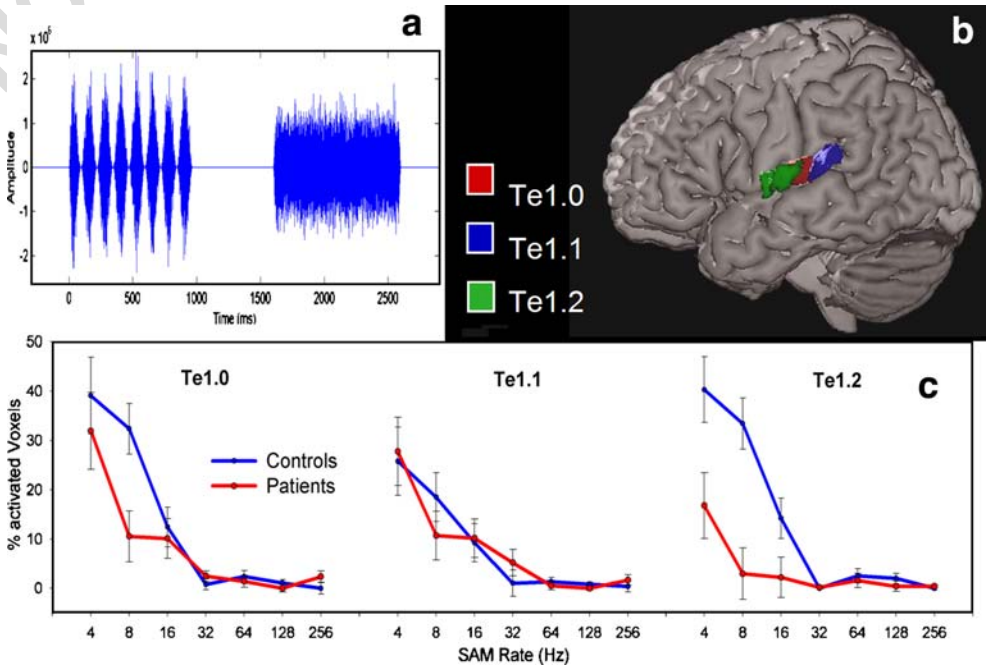

Fig. 5 Sinusoidally amplitude modulated (**a**-Left) and unmodulated (**a**-Right) broadband-noise used in current psychophysical and fMRI studies. **b** Three cytoarchitecturally distinct subdivisions of primary auditory cortex or Heschl's Gryus (Morosan et al. 2001). **c** Extent of BOLD activation in controls and patients with schizophrenia as a function of SAM rate for each cytoarchitectural defined auditory region (n=18 in each group, p<0.001; Budd, Michie, Schall, Cooper and Case, in preparation)

particularly pronounced for the temporal characteristics of sounds (Umbricht and Krljes 2005) early in the course of the illness (Todd et al. 2008). We are exploring aspects of this assertion in a number of different ways. For example, we employed a combination of psychoacoustic and fMRI methods to determine whether psychoacoustic sensitivity to auditory temporal information was apparent in the pattern of brain to temporal variations in sound. To achieve this we used sinusoidally amplitude modulated (SAM) broadband noise (see Fig. 5a) to activate auditory cortical areas. BOLD activity in anterolateral regions of auditory cortex showed a similar sensitivity to SAM rate as observed for psychophysical thresholds obtained for the same participants. The preliminary results of a study in progress found that reduced BOLD activity in these same anterolateral regions of auditory cortex in patients was associated with a reduction in psychophysical sensitivity to SAM rate relative to healthy controls. A cytoarchitectural analysis of these auditory cortical regions (Fig. 5b) implicates the involvement of functionally-specific subdivisions in auditory cortex in cortical sensitivity to auditory temporal stimulation (Fig. 5c). Based on previous fMRI evidence of binaural specialisation in auditory cortical regions (Budd et al. 2003), our current schizophrenia research is examining

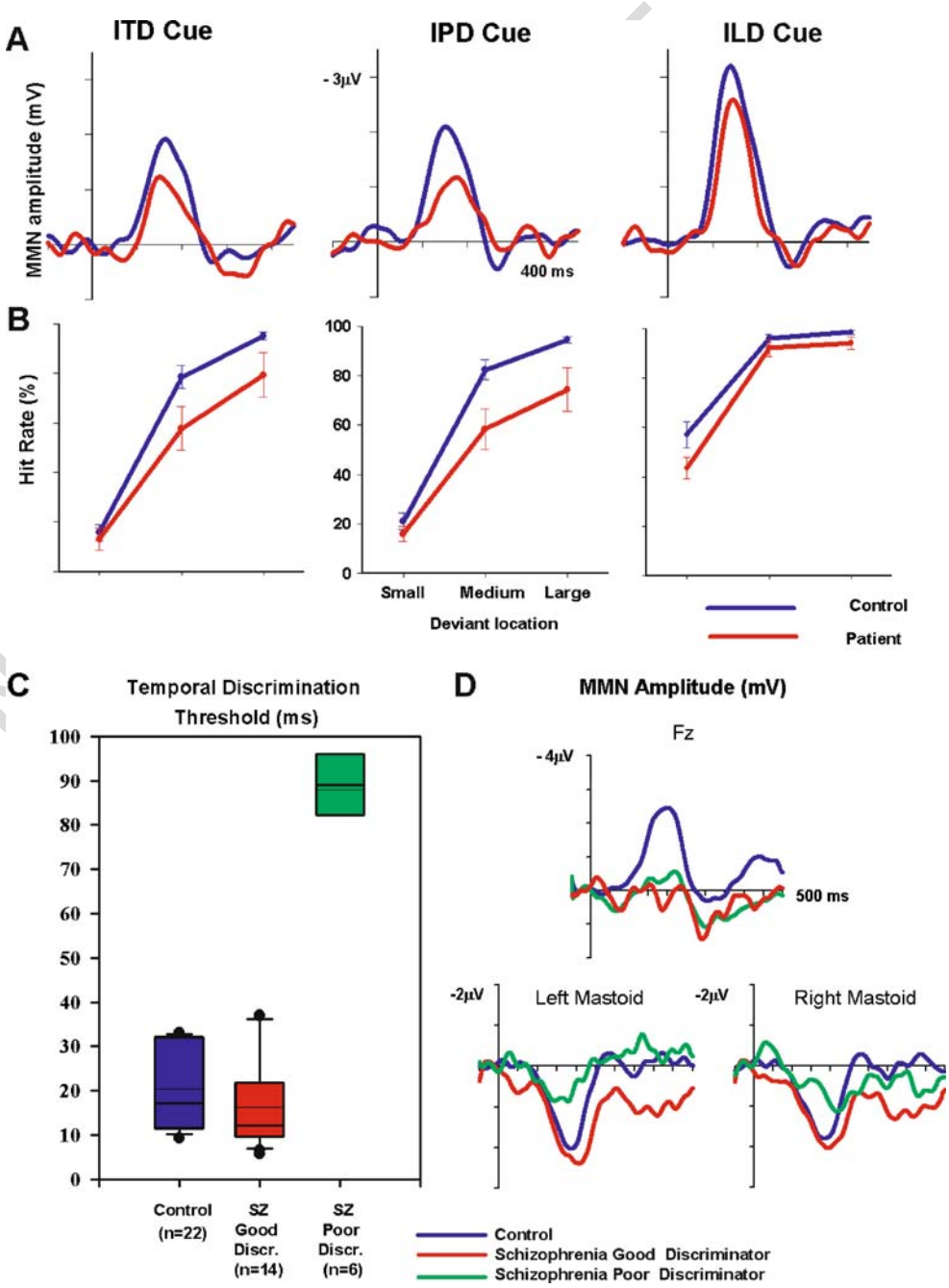

Fig. 6 **a** MMN amplitude (in micro volts) at Fz for the *ITD*, *IPD*, and *ILD* conditions for individuals with schizophrenia and controls. Data for the right side deviant condition only from Matthews et al (2007) are shown; **b** Behavioural detection ability (hit rate) for the *ITD*, *IPD* and *ILD* tasks for individuals with schizophrenia and controls (Modified from Matthews et al. 2007); **c** Temporal discrimination thresholds for controls, and patients who exhibited a bi-modal distribution with some patients being good discriminators and others having very poor discrimination (high thresholds); **d** comparison of the nose-referenced mismatch negativity waveforms at Fz and the mastoids for 3 groups: controls, patients who produced high threshold estimates (poor patient discr.) and patients who performed equivalently to controls on interval discrimination (good patient discr.) (Modified from Todd et al. 2003)

cortical and psychophysical changes in responses to acoustic stimulation where interaural characteristics are manipulated. These data will allow a better determination of the level within the ascending auditory system where neurophysiological changes associated with auditory temporal processing deficits in schizophrenia arise.

Interaural characteristics have also been manipulated in an MMN study of sound lateralization in patients (Matthews et al. 2007) that targeted temporal processing deficits. This approach took advantage of the fact that there are two major types of interaural cues that the auditory system employs to provide information about the spatial location of a sound: temporal cues of which there are two types-interaural differences in the arrival time (ITD), and in the ongoing phase (IPD) of the sound wave reaching the two ears; and non-temporal cues-interaural differences in loudness (ILDs) due to the acoustic shadow cast by the head. We recorded MMN to sounds that were deviant in spatial location based on changes to ITD, IPD or ILD of the sound. As shown in Fig. 6a and b, individuals with schizophrenia had reduced MMN amplitudes, and reduced target detection rates for spatial deviants created using the two temporal cues (ITD and IPD), but showed no impairment in the use of non temporal cues (ILD). These findings provide strong evidence in support of the suggestion that temporal processing is particularly impaired in schizophrenia.

However, the integration of psychophysical and MMN measures in another study (Todd et al. 2003) suggests a more complex story. In a paradigm that measured MMN to sounds that differed in extent (duration), only those patients who had particularly high discrimination thresholds for distinguishing temporal extents (Fig. 6c) exhibited reduced (phase-reversed) MMNs at the mastoids, whereas both patient groups, those with poor and those with good discrimination thresholds, showed reduced MMN at frontal sites (Fig. 6d) Based on these results, it appears that poor temporal processing is unlikely to be the only cause of MMN reduction in schizophrenia in this paradigm and that other factors such as insensitivity to the acoustic context may also contribute.

Summary

Although we can claim some success in our integrative endeavors, we have had less success with some of the more obvious integrative approaches. There has been substantial speculation on the possibility of integrating fMRI and ERP methodologies in order to achieve both high spatial and high temporal resolution of cortical activity. A current study into the cortical sources of MMN (Fig. 4a) has demonstrated the viability of incorporating individual differences in cortical anatomy, as revealed by structural MRI, into the ERP source modelling process. Constructing individual head models and utilising the location and orientation of the cortical surface as source model constraints is technically challenging, but conceptually sound, and produces results that have good face validity. However we, like many research groups, had naive expectations of being able to utilise fMRI foci as seeds for ERP source models. This is technically easy to achieve, but conceptually more difficult to justify. There are many reasons to suspect that activity visible with one methodology may be invisible to the other. For example, fMRI may be responsive to event-related synchronisation/desynchronisation, a cortical process which is not directly assessed by ERPs. A more promising approach that we have been exploring appears to be an examination of the intercorrelation between ERP components, heamodynamic responses, and behavioural data, both within and across subjects. However, this approach requires more sophisticated experimental designs.

Many challenges remain – we need to understand in more detail the computations associated with BOLD activation of a particular region or an ERP component, a task that requires collaboration with cognitive scientists with expertise in computational models of cognition. Such collaborations are already underway using formal models of decision making applied to task switching paradigms. Further, to investigate coordination between brain regions contributing to large scale networks supporting cognition, we need to add structural connectivity analysis based on diffusion tensor imaging (DTI). The successor to the VBB, the ASRB, incorporates DTI data as a means of examining anatomical connectivity and the microstructure of white matter in vivo.

While this brief overview of ongoing neuroimaging research being conducted at Newcastle with our Pacific Rim colleagues cannot be said to have provided a coherent account of the neurobiology of the disorder of schizophrenia, we believe that these examples of integration have enhanced our understanding of structure-function relationships and revealed in some instances the neural network of key brain regions contributing to both normal and abnormal cognition. It has not been an exercise in carrying coals in Newcastle by us or our Pacific Rim collaborators!

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