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The mismatch negativity: an index of cognitive decline in neuropsychiatric and neurological diseases and in ageing

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Cognitive impairment is a core element shared by a large number of different neurological and neuropsychiatric diseases. Irrespective of their different aetiologies and symptomatologies, most appear to converge at the functional deficiency of the auditory-frontal cortex network of auditory discrimination, which indexes cognitive impairment shared by these abnormalities. This auditory-frontal cortical deficiency, and hence cognitive decline, can now be objectively measured with the mismatch negativity and its magnetic equivalent. The auditory-frontal cortical network involved seems, therefore, to play a pivotal, unifying role in the different abnormalities. It is, however, more likely that the dysfunction that can be detected with the mismatch negativity and its magnetoencephalographic equivalent manifests a more widespread brain disorder, namely, a deficient N-methyl-D-aspartate receptor function, shared by these abnormalities and accounting for most of the cognitive decline.

Introduction

In all major neuropsychiatric and neurological disorders, with different aetiologies and symptomatologies, there seems to exist a common core, i.e. cognitive impairment. For instance, in schizophrenia, there is often a gradual cognitive and functional decline (Umbricht and Krljes, 2005). Cognition is also affected in bipolar disease (Thompson *et al.,* 2005), stroke (Ilvonen *et al.,* 2003; Dhawan *et al.,* 2010), epilepsy (Boatman *et al.,* 2008; Kaaden and Helmstaedter, 2009), Parkinson's disease (Rongve and Aarsland, 2006), multiple sclerosis (Jung *et al.,* 2006), Alzheimer's disease and other neurodegenerative brain disorders. In addition, cognition is also affected in ageing (Cansino, 2009) and, for example, in patients with HIV infection (Schroeder *et al.,* 1994) and in survivors of coma (Fischer *et al.,* 2004) and the persistent vegetative state (Wijnen *et al.,* 2007). Importantly, in almost all of these cases, this cognitive decline seems to be indexed by temporofrontal functional deficiency expressed as deficient auditory discrimination and orienting.

This functional deficiency, and hence cognitive decline, can now be objectively assessed, even in the absence of the patient's attention and task performance, by means of a relatively simple electrophysiological measure, the mismatch negativity (MMN; Näätänen *et al.,* 1978). The MMN is generated by the temporofrontal network of automatic auditory change (or regularity-violation) detection (Alain *et al.,* 1998), and its magnetoencephalographic equivalent, magnetoencephalographic MMN (Hari *et al.,* 1984), even in the absence of attention (in fact, the MMN is usually recorded under ignore conditions, with the subject or patient, for example, watching videos or reading a book). This is a major advantage of the MMN relative to other cognitive event-related potentials such as the P3 (Sutton *et al.,* 1965), which depend on attention and cannot therefore be reliably used in several clinical populations. The magnetoencephalographic MMN selectively reflects the temporal component of the MMN since magnetoencephalography is insensitive to the frontal generators of the MMN (Hämäläinen *et al.,* 1993). Therefore, the magnetoencephalography is particularly well-suited for detecting cognitive deficits specific for the temporal lobes. The combined use of the electroencephalography and magnetoencephalography recordings help to determine to what extent the temporal and frontal MMN components are impaired, since with electroencephalography, both components can be detected (Hämäläinen *et al.,* 1993).

Figure 1 illustrates that the MMN indexes the behavioural discrimination accuracy. In addition, the MMN can also index sensory–memory traces (their duration, accuracy and capacity) formed on the basis of the preceding stimulation, that provide the necessary prerequisite for the detection of change (regularity-violation) (Näätänen *et al.,* 2007). In this review, we firstly show that this functional deficit indexed by the MMN and the magnetoencephalographic MMN reflects cognitive decline in the different neuropsychiatric and neurological abnormalities and in ageing. Thereafter, we will review converging evidence indicating that the auditory neural function involved is enhanced by different cognition-enhancing drugs and is dampened by drugs
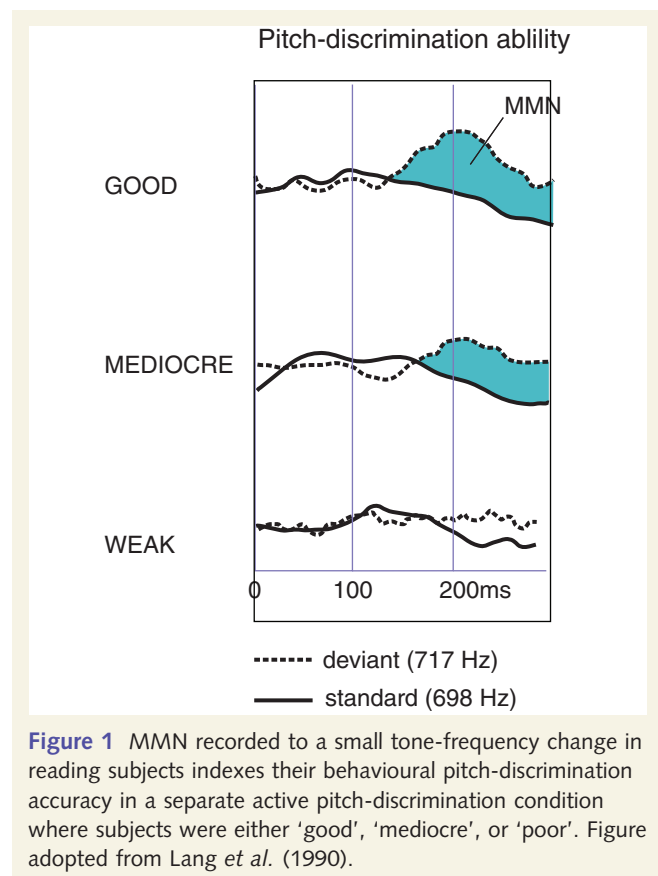

Figure 1 MMN recorded to a small tone-frequency change in reading subjects indexes their behavioural pitch-discrimination accuracy in a separate active pitch-discrimination condition where subjects were either 'good', 'mediocre', or 'poor'. Figure adopted from Lang *et al.* (1990).

decreasing cognitive performance and, further, that it reflects cognitive variation even in normal healthy individuals. In addition, we will also review relevant data involving the visual-modality analogy of the auditory MMN. To complement our personal collections forming the literature basis of the present review, we also conducted a literature search with terms 'mismatch negativity and cognition' and included all studies published in English-language refereed journals, from 2005–2010, that report clinical data pertinent to the MMN–cognition relationship. To sharpen the focus of the review, we have, however, omitted the extensive developmental literature.

The MMN is generated by a temporofrontal network of auditory change detection, in which bilateral auditory-cortex activation, underlying pre-perceptual change detection, triggers—with a very short time delay (Rinne *et al.,* 2000)—a predominantly right hemispheric frontal process associated with involuntary attention switch to auditory change (Näätänen and Michie, 1979; Giard *et al.,* 1990; Rinne *et al.,* 2005, 2006). Consequently, the MMN has two overlapping subcomponents, one bilaterally and feature-specially generated (Rosburg, 2003) by the auditory cortices (the supratemporal MMN subcomponent) and the other by the frontal cortex (the frontal MMN subcomponent). In magnetoencephalographic MMN recordings, only the supratemporal component can be seen, with the radially oriented frontal component being absent. In contrast, both subcomponents have their functional MRI (Celsis *et al.,* 1999; Schall *et al.,* 2003; Molholm *et al.,* 2005; Opitz *et al.,* 2009), PET (Tervaniemi *et al.,* 2000; Dittmann-Balcar *et al.,* 2001; Müller *et al.,* 2002) and

optical-imaging (Tse and Penney, 2008) equivalents. Furthermore, the MMN has its equivalents in other sensory modalities too [the visual MMN (Alho *et al.,* 1992; Tales *et al.,* 1999, 2002; Heslenfeld, 2003; Pazo-Alvarez *et al.,* 2003; Czigler 2007); the somatosensory MMN (Kekoni *et al.,* 1997); and the olfactory MMN (Krauel *et al.,* 1999)], and can also be recorded in different animals [e.g. in monkey (Javitt *et al.,* 1992); cat (Csepe *et al.,* 1987; Pincze *et al.,* 2001, 2002); rat (Astikainen *et al.,* 2006; Ruusuvirta *et al.,* 2007); guinea pig (Kraus *et al.,* 1994); and mouse (Umbricht *et al.,* 2005; Ehrlichman *et al.,* 2008)]. Recently, it was shown by Restuccia *et al.* (2009) and Spackman *et al.* (2010) that, similarly to the auditory MMN, the somatosensory MMN, too, has sensory-specific (somatosensory cortex) and frontal subcomponents.

Sometimes, reliable MMN data cannot be obtained, usually because of a weak signal-to-noise ratio. Moreover, even though the MMN procedure usually provides satisfactory, and often excellent results at the group level, much work is still needed until the MMN can reliably be used in the objective assessment of discrimination of individual subjects and patients. Fortunately, considerable progress toward this end has recently been made (e.g. Marco-Pallares *et al.,* 2005; Kalyakin *et al.,* 2007, 2008*a, b*, 2009; Cong *et al.,* 2009, 2010*a, b*).

Neuropsychiatric disorders

Schizophrenia

Shelley *et al.* (1991), in a pioneering study, found that the MMN amplitude for an occasional duration increment of a repetitive tone was considerably attenuated in patients with schizophrenia compared with that of controls, suggesting that patients' duration discrimination was compromised. Javitt (1993), in turn, was the first to demonstrate frequency-MMN deficiency in patients with schizophrenia. The duration-MMN deficit was subsequently corroborated by Catts *et al.* (1995) and Michie *et al.* (2000). Michie (2001) also found that the MMN abnormalities for duration change, particularly those for duration increments, were even more robust than those for frequency change (Davalos *et al.,* 2003). Importantly, Catts *et al.* (1995) found that in bipolar patients, the duration-change MMN was not affected, suggesting the specificity of the duration-MMN deficiency in patients with schizophrenia. Fisher *et al.* (2008), who recorded five different MMNs in parallel (Näätänen *et al.,* 2004; Thönnesen *et al.,* 2008), reported that the MMN attenuation for duration decrement only occurred in patients with schizophrenia with auditory hallucinations.
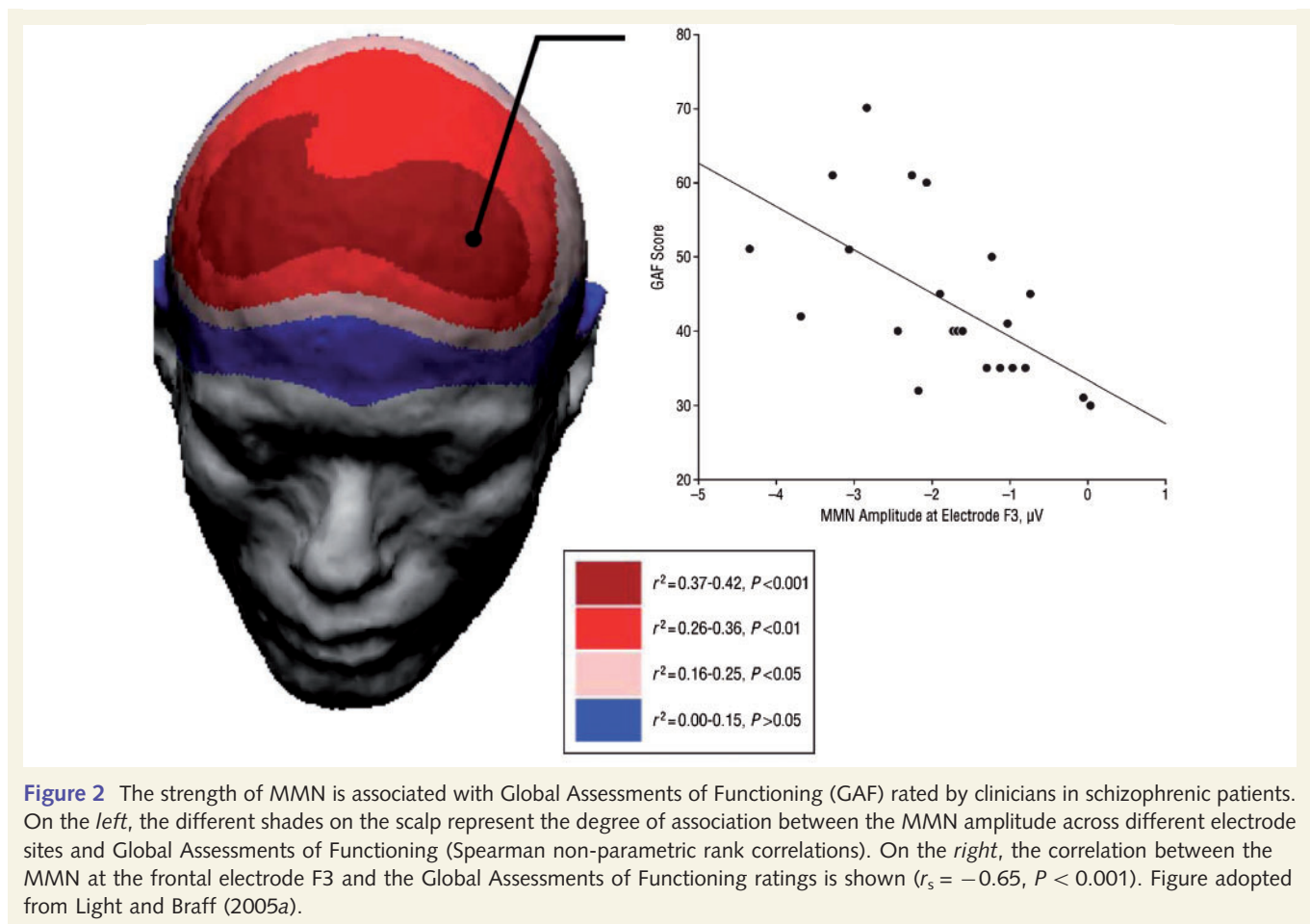
In the meta-analysis of Umbricht and Krljes (2005), most of the 32 MMN studies published by the end of 2003, meeting the inclusion criteria, showed that schizophrenia is associated with a MMN-amplitude decrease for frequency or duration changes. There was also a systematic increase in the effect size of the MMN deficit as a function of illness duration, indicating that this attenuation reflects disease progression.

A correlation of the MMN deficit for tone-duration increment with neuropsychological impairment (as indexed by Digit Span Test and Rivermead Behavioural Memory Test) in patients with chronic schizophrenia was reported by Baldeweg *et al.* (2004). These authors introduced a novel paradigm, the so-called roving paradigm (in which the standard is frequently replaced by another), to schizophrenia research, which seemed to provide a better index for the degree of cognitive impairment of patients than that provided by the traditional constant-standard paradigm. Furthermore, Light and Braff (2005*a*) showed that the MMN deficit for tone-duration prolongation specifically indexes gradual functional deterioration; there was a strong correlation between the clinical ratings on the Global Assessment of Functioning and the MMN amplitude in these patients (Fig. 2). Moreover, the MMN was highly predictive of patients' level of independence in their community-living situations. The authors concluded that '... the MMN deficits represent a core neurophysiological dysfunction that is linked to global impairments in everyday functioning in patients with schizophrenia' (Light and Braff, 2005*a*, p. 127). Furthermore, this correlation between the MMN deficit and the Global Assessment of Functioning ratings was replicated in longitudinal studies 1–2 years later, indicating a stable relationship (Light and Braff, 2005*b*). For corroborating results, see Hermens *et al.* (2010). Interestingly, this relationship was also found in normal healthy subjects (Light *et al.,* 2007).

Subsequently, using a visual-MMN paradigm, Urban *et al.* (2008) found that patients with schizophrenia below the median on the Global Assessment of Functioning ratings had smaller visual-MMN amplitudes for change of the direction of a peripheral movement than normal controls and patients who were above the median on the Global Assessment of Functioning ratings. Moreover, Wynn *et al.* (2010) found that the (auditory) MMN for duration increment can also index social cognition and functioning in patients with schizophrenia. Further evidence for the MMN-cognition relationship in patients with schizophrenia was provided by Turetsky *et al.* (2009). Umbricht *et al.* (2006) found that first-episode patients, in general, did not show an attenuated MMN for tone-frequency and -duration changes except for those with a low premorbid educational level.

The results of Baldeweg *et al.* (2002, 2004) and Sato *et al.* (2003) suggested that the frontal generator of the MMN in particular is affected in schizophrenia. This pattern of results, interpreted by Baldeweg *et al.* (2002) as reflecting a dampened frontal involuntary attention-switching function, correlated with the negative symptoms in the Baldeweg *et al.* (2004) study. For corroborating results, see Sato *et al.* (2003). This dampening of the frontal involuntary attention-switching function might, according to Näätänen and Kähkönen (2009), contribute to patients' negative symptoms (such as social withdrawal) by diminishing involuntary attention switches to socially relevant auditory cues such as stress and loudness, changes in speaker voice, or the change from one speaker to another (Oades *et al.,* 1996; Javitt *et al.,* 1998). Consistent with this, Matthews *et al.* (2007) obtained MMN and behavioural data for change of the locus of sound origin suggestive of a selective impairment in the encoding of inter-aural time cues in patients with schizophrenia. The authors proposed that this impairment could have a detrimental effect on a patient's ability to locate sounds in natural settings, and thus it could contribute to their social communication problems. In particular, as spatial loci of origin of sounds function as a central cue when

Figure 2 The strength of MMN is associated with Global Assessments of Functioning (GAF) rated by clinicians in schizophrenic patients. On the *left*, the different shades on the scalp represent the degree of association between the MMN amplitude across different electrode sites and Global Assessments of Functioning (Spearman non-parametric rank correlations). On the *right*, the correlation between the MMN at the frontal electrode F3 and the Global Assessments of Functioning ratings is shown ($r_s = -0.65$, $P < 0.001$). Figure adopted from Light and Braff (2005*a*).

selectively attending to a certain speaker in the presence of multiple speakers, any decline in the capacity to use spatial cues will interfere with the ability to control the focus of attention effectively and further impair communication skills.

On the basis of such evidence, Näätänen and Kähkönen (2009), regarding it unlikely that the structural (Hirayasu *et al.*, 1998; Salisbury *et al.*, 2007) and functional central auditory system changes occurring in patients with schizophrenia directly cause the cognitive and functional decline, suggested that it might be the cognitive, intellectual deprivation (in analogy to sensory deprivation) that gradually leads to the long-term cognitive and functional loss. According to these authors, this deprivation would be caused by the blurring of the auditory input, and by the dampening of the automatic attention-switching function supporting the adequate reception and analysis of speech-related and other auditory stimulation and thus the continuous contact with the environment (Shenton *et al.*, 1997; Toyomaki *et al.*, 2008).

Magnetoencephalographic studies (e.g. Kreitschmann-Angermahr *et al.*, 1999, 2001; Thønnesen *et al.*, 2008) have also shown a magnetoencephalographic MMN deficit for auditory change in patients with schizophrenia, indicating the involvement of the auditory cortices too, in particular the left auditory cortex (Hirayasu *et al.*, 2000), in the magnetoencephalographic MMN deficit of these patients.

Subsequently, the relationship between the MMN for tone-duration increment and the functional status of patients

with schizophrenia was also found by Kiang *et al.* (2007) who reported that this MMN deficiency was associated with proverb-interpretation abnormalities and deficits in auditory verbal memory. In addition, Rasser *et al.* (2011) found that MMN deficit for tone-frequency change indexed low socio-occupational function levels of the patients. This frequency-MMN deficit also indexed widespread cortical grey matter loss not only in the left hemisphere Heschl's gyrus but also in the motor and executive regions of the frontal cortex, while MMN-amplitude reduction for duration increment also correlated with grey matter loss in the right Heschl's gyrus. Kawakubo *et al.* (2007) showed that, in patients with schizophrenia, the MMN to across-phoneme change (but not that to tone- or phoneme-duration prolongation) was predictive of the acquisition of social skills during a 3-month social skills training programme. In addition, Toyomaki *et al.* (2008) found that MMN deficits for tone-duration increment in patients with schizophrenia were related to impairments in executive functioning. Moreover, Kawakubo *et al.* (2006) observed that MMN deficit for duration decrement of a speech sound (but not that of a simple tone) predicted verbal memory deficits in these patients.

Further, medication did not abolish MMN abnormality in patients with schizophrenia (Catts *et al.*, 1995; Schall *et al.*, 1998; Umbricht *et al.*, 1998, 1999; Korostenskaja *et al.*, 2005). Moreover, the MMN deficit was present irrespective of the stimulus-onset-asynchrony used (Javitt *et al.*, 1998), indicating

that it is the memory-trace formation (and thus perception; Näätänen and Winkler, 1999) that is affected rather than memory-trace duration. Consequently, this data pattern is orthogonal to that obtained in patients with Alzheimer's disease who show a normal MMN with short stimulus-onset-asynchronies, suggesting normal memory-trace formation and perception, but no MMN with long stimulus-onset-asynchronies such as 3 s, indicating that their sensory-memory trace duration is abnormally short (Pekkonen *et al.*, 1994).

The MMN amplitude is also attenuated in different (healthy) schizophrenia risk groups, such as individuals with velo-cardio-facial (DiGeorge) syndrome (Baker *et al.*, 2005), healthy first-order relatives of patients with schizophrenia (Jessen *et al.*, 2001; Michie *et al.*, 2002), prodromal subjects (Brockhaus-Dumke *et al.*, 2005), subjects with an 'ultra-high' risk of schizophrenia (Shin *et al.*, 2009), and children at 'high' risk for schizophrenia (Schreiber *et al.*, 1992). Importantly, it was recently shown by Bodatsch *et al.* (2011) that the duration-decrement MMN of high-risk individuals predicted who of them would convert to first-episode psychosis within 2 years and when this might happen. These results consequently contribute not only to the prediction of conversion but also to a more individualized risk estimation and thus risk-adopted prevention.

Bipolar disease

In contrast to schizophrenia, bipolar disease is usually not associated with MMN attenuation (Catts *et al.*, 1995; Umbricht *et al.*, 2003; Hall *et al.*, 2007, 2009; Salisbury *et al.*, 2007; Takei *et al.*, 2010). Takei *et al.* (2010), however, found that the magnetoencephalographic MMN peak latencies for tone-duration increment and frequency change were prolonged in the right hemisphere of patients with bipolar disease, in comparison with those of controls. There was also an equivalent-current-dipole location difference in the left hemisphere between the patients and controls. Andersson *et al.* (2008), studying patients with bipolar II disorder, found that their MMN for tone-duration decrement was attenuated in amplitude and prolonged in latency in comparison to that of controls and, further, that patients performed worse than controls in different neuropsychological tasks. Reite *et al.* (2009) recently described structural and functional auditory-cortex abnormalities in bipolar patients which, according to the authors, may relate to the cognitive impairments found in these patients (Bruder *et al.*, 1975, 1981, 1994).

Chronic alcoholism

Chronic use of alcohol induces neurotoxicity and results in cognitive impairment (Campanella *et al.*, 2009), particularly in that associated with the frontal-cortex functioning (Pfefferbaum *et al.*, 1997; George *et al.*, 2001; Polo *et al.*, 2003; Park *et al.*, 2010). Kathmann *et al.* (1995) reported delayed MMN peak latencies in chronic alcoholics, in comparison with their healthy peers. Polo *et al.* (1999) found MMN attenuation for tone-frequency change in patients relative to age-matched control subjects, particularly after a certain critical age, of ∼40 years.

Furthermore, this MMN deficiency was increased with age and was more prominent when a longer (2 s) than shorter (0.75 s) stimulus-onset asynchrony was used, suggesting the presence of an additional effect of alcoholism in the form of the accelerated age-related shortening of the auditory sensory-memory duration (Polo *et al.*, 1999; Grau *et al.*, 2001).

Neurological and neurodegenerative disorders

Stroke and aphasia

In patients with stroke, a focal cerebral infarction in the affected core territory is often accompanied by damage even in brain regions that can be quite remote from the locus of infarction (including even contralateral regions), explaining, in part, the widespread cognitive and other neurological defects in these patients (Biegon *et al.*, 2004; Dhawan *et al.*, 2010). In addition, the MMN in these patients is considerably attenuated in amplitude, correlating with the cognitive loss, and permitting the objective monitoring of the latent post-stroke recovery process when reliable behavioural measurements are not yet possible (Ilvonen *et al.*, 2003). Ilvonen *et al.* (2003) found that at 4 and 10 days after left-hemisphere stroke onset, patients' sound discrimination was impaired in their left hemisphere, as suggested by attenuated MMNs for duration and frequency change in a harmonically rich tone, especially when presented to the right ear. At 3 months after stroke onset, the MMN for right-ear duration change had considerably increased in amplitude, and was again of approximately normal size. Moreover, a remarkable increase in the left-ear frequency MMN was observed between 3 and 6 months post-stroke. During the follow-up period, progressive improvement in speech comprehension test scores was also found. There was a close relationship between the duration-MMN amplitude increase and improvement in the Boston Diagnostic Aphasia Examination speech-comprehension test from 10 days to 3 months post-stroke.

Särkamö *et al.* (2010a), dividing their 60 middle cerebral artery stroke patients into music and audio-book listening and control groups, recorded their magnetoencephalographic MMN to frequency and duration changes in a binaurally delivered complex tone (in addition, all patients received normal hospital treatment and rehabilitation of stroke patients). It was found, as expected, that the magnetoencephalographic MMN amplitudes were generally smaller in the lesioned than opposite hemisphere. Importantly, the frequency-magnetoencephalographic MMN amplitude increased more in both music and audio-book groups than in the control group during the 6-month post-stroke period (Fig. 3). In addition, the duration-magnetoencephalographic MMN amplitude increased more in the audio-book group than in the other groups. The frequency-magnetoencephalographic MMN amplitude increase correlated with the behavioural improvement of verbal memory and focused attention induced by music listening. The authors interpreted their results as demonstrating that merely listening to music or speech starting early in
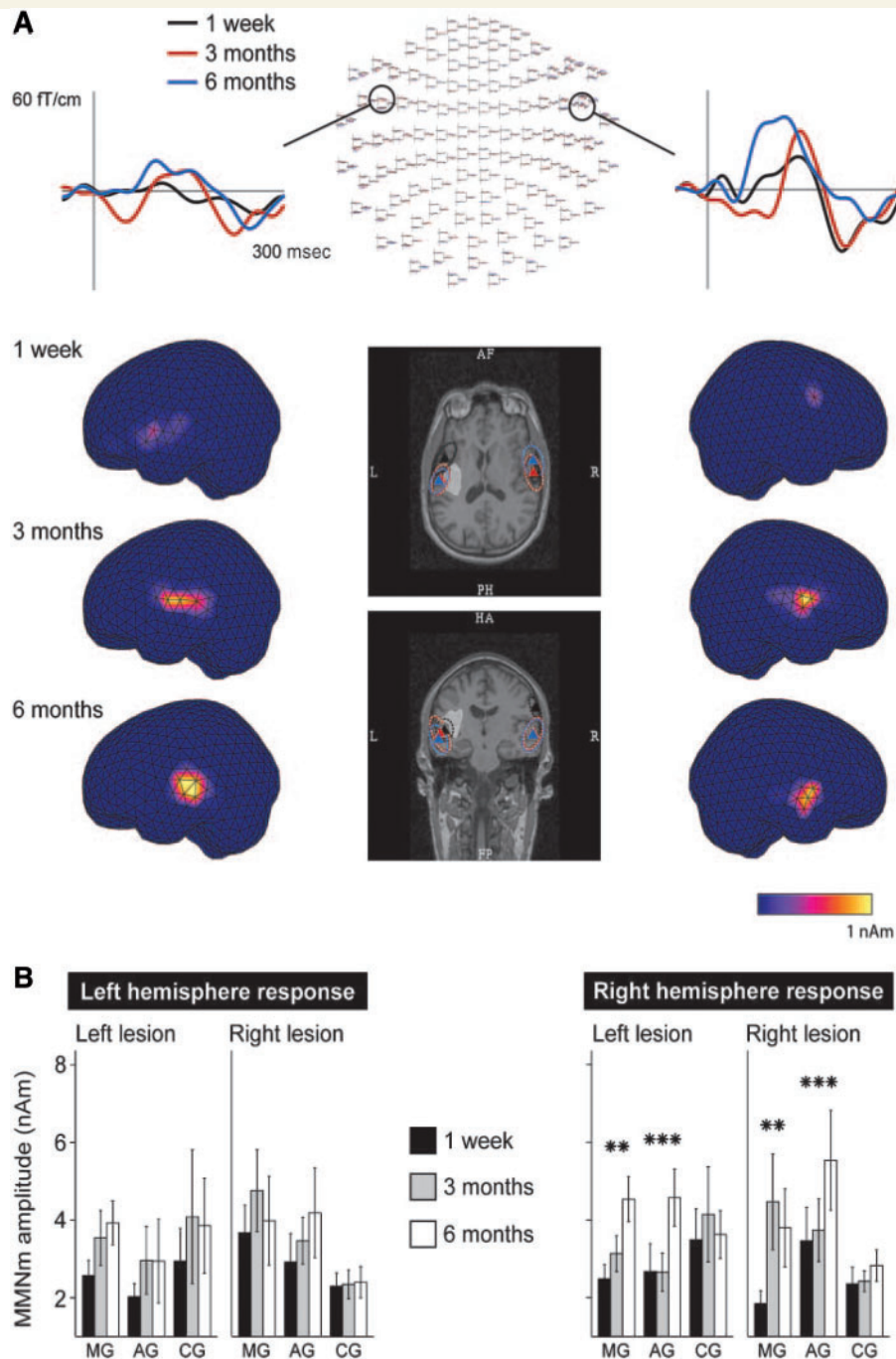
Figure 3 The tone-frequency magnetoencephalographic MMN (MMNm) at different stages of stroke recovery. (**A**) A case example illustrating the typical post-stroke recovery of the magnetoencephalographic MMN. Changes in the strength of the magnetoencephalographic MMN response in the left and right hemispheres are shown by difference waves from individual magnetoencephalographic channels over the temporal lobes. The magnetic resonance images in the middle of the figure show the lesioned area (white). (**B**) Across-patient results of the strength of the frequency-magnetoencephalographic MMN source in the left and right hemispheres. Data are shown separately for the left- and right-hemisphere patients. AG = audio book group; CG = control group; MG = music group. From Särkämö *et al.* (2010*a*).

the post-stroke period can induce long-term plastic changes in early sensory processing, as reflected by the magnetoencephalographic MMN enhancement, which, in turn, may facilitate the recovery of higher cognitive functions. These remarkable results

encourage the use of music and speech stimulation in the early post-stroke period.

In another study Särkämö *et al.* (2010*b*; see also Särkämö *et al.*, 2009) addressed amusia caused by left or right middle cerebral

artery stroke. They found that amusia caused by right hemisphere damage, especially that to temporal and frontal areas, was more severe than that caused by left hemisphere damage. Furthermore, the severity of amusia correlated with weaker frequency-magnetoencephalographic MMN responses in amusic right hemisphere patients. Within the right hemisphere-damage group, the amusic patients who had damage in the auditory cortex showed worse recovery from amusia as well as weaker magnetoencephalographic MMN responses throughout the 6-month follow-up than did the non-amusic patients or the amusic patients with no auditory-cortex damage. The amusic patients (both with and without auditory-cortex damage) performed worse than the non-amusic patients on a number of tests of different aspects of cognitive performance (including working memory, attention and cognitive flexibility). These findings suggested, according to the authors, domain-general cognitive deficits as the primary mechanism underlying amusia without auditory-cortex damage, whereas amusia with auditory-cortex damage is associated with both auditory and cognitive deficits. Previously, Kohlmetz *et al.* (2001) found a gross frequency-MMN amplitude reduction in left hemispheric stroke patients with amusia whereas left hemispheric stroke patients with no amusia showed a normal-sized MMN.

Auther *et al.* (2000) found that the presence of the MMN for speech-sound change indicated better auditory comprehension than did MMN absence. In addition, poor comprehension and MMN absence were related to temporal-lobe lesions. Subsequently, Pettigrew *et al.* (2005) found a strong correlation between the MMNs both to complex-tone duration decrement and consonant-vowel syllable change (from word to non-word and *vice versa*) with auditory comprehension. Such complex changes appear to be better in separating aphasic patients from control subjects than simple tone-frequency changes (Aaltonen *et al.*, 1993; Csepe *et al.*, 2001). Wertz *et al.* (1998) found that the MMN for speech-sound (consonant-vowel syllable) change was present in 100% of control subjects, whereas it was present only in 54% of aphasic subjects. Among those patients who showed this response, the MMN duration was shorter with more severe aphasia on The Western Aphasia Battery, Porch Index of Communicative Ability and The Token Test.

Multiple sclerosis

Jung *et al.* (2006), studying 46 patients with multiple sclerosis, found that, besides the exogenous N1–P2 complex, the MMN and P3a for duration decrement were attenuated in amplitude in patients with multiple sclerosis, concluding that these changes might suggest that patients with multiple sclerosis are prone to pre-attentive auditory information processing deficits, besides previously described controlled processing difficulties (Kujala *et al.*, 1995; Foong *et al.*, 1999). In addition, the N1–P2 complex alterations might, according to these authors, signify that the basic cortical auditory processing is altered in multiple sclerosis. The MMN was considerably smaller in amplitude in patients showing cognitive decline (assessed by using a battery of cognitive tests) than in those with no cognitive decline (Fig. 4). The authors concluded that MMN alterations may represent an objective index of cognitive disturbances in patients with multiple sclerosis.
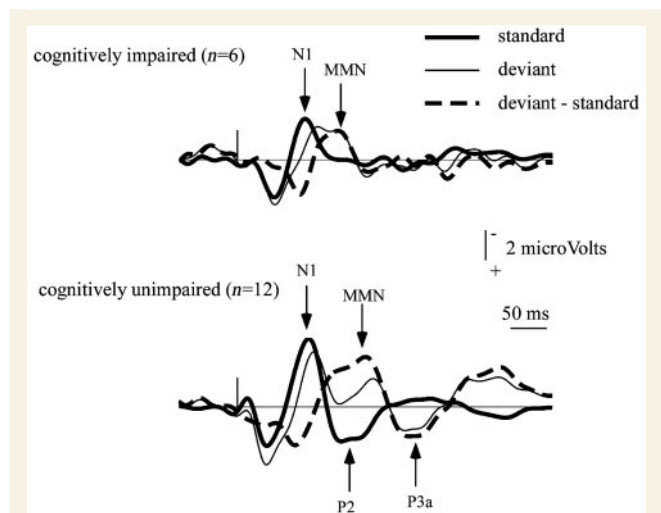

Figure 4 Neural responses reflecting cognitive decline in multiple sclerosis. In patients with cognitive impairment (*top*), the N1 and MMN responses are considerably smaller in amplitude than those of patients with no cognitive impairment (*bottom*). Adapted from Jung *et al.* (2006).

Consistent with this, Santos *et al.* (2006) found that the absence of the MMN for tone-duration decrement in patients with multiple sclerosis was closely related to cognitive impairment, assessed with the Paced Auditory Addition Test, observed in some of the patients. Similar results were also obtained with the frequency MMN, corroborating the previous results of Gil *et al.* (1993). In patients with no cognitive decline, the MMN response was similar to that in healthy control subjects.

Velo-cardio-facial syndrome

Individuals with the velo-cardio-facial (DiGeorge) syndrome (Goldberg *et al.*, 1993), who have a greatly increased schizophrenia risk (Baker *et al.*, 2005), also show an MMN deficit. It was found by Baker *et al.* (2005) that the MMNs for different speech-sound and non-speech-sound changes of adolescents and young adults with the velo-cardio-facial syndrome were considerably attenuated in amplitude. Moreover, these MMN effects were considerably stronger and the cognitive deficiencies more severe in the subjects with velo-cardio-facial syndrome carrying the COMT108/158Met allele (a greater risk of schizophrenia) than the COMT108/158Val allele (a smaller risk of schizophrenia).

Epilepsy

Studying children of 7–11 years of age with benign rolandic epilepsy, Boatman *et al.* (2008) found that in approximately half of them, the MMN to speech-sound change was absent and its peak latency was prolonged in the remainder of the patients. Those who had no MMN for speech sounds also had the most severe cognitive impairments on behavioural testing. Liasis *et al.* (2001) found no MMN to syllable change in children with benign rolandic epilepsy, who usually suffer from language

difficulties (Staden *et al.*, 1996). Borghetti *et al.* (2007), studying adult patients with epilepsy, obtained some frequency-MMN results suggesting that the MMN could be used as an index of the improvement of pre-attentive central processing in audition as a result of the implantation of a vagus-nerve stimulator.

Korostenskaja *et al.* (2010), using the five features MMN paradigm of Näätänen *et al.* (2004), found that the magnetoencephalographic MMN of their patients with a mean age of 13 years was attenuated in amplitude for each of these deviations (tone duration, frequency, intensity, perceived locus of origin, silent gap in the middle of the tone). Lin *et al.* (2007) found that the magnetoencephalographic MMN peak latency for tone-duration decrement in young adult patients was longer than that of the controls. Interestingly, the magnetoencephalographic MMN was accompanied and temporally overlapped by a phase-locking response of alpha and theta oscillations (revealed by using a wavelet-based analysis). In the five patients who subsequently became seizure-free after the successful surgical removal of right temporal epileptic focus, the phase-locking response was enhanced in amplitude, which did not occur in patients with a less successful surgical operation.

Dementia, Alzheimer's disease and Huntington's disease

Schroeder *et al.* (1995) found that the MMN to novel stimuli was delayed in peak latency in all elderly subjects compared with that of the young. Further, it was smaller in amplitude in the demented than non-demented elderly subjects. The MMN for frequency change was smaller only in the low-functioning but not in the high-functioning elderly, compared with that of the young. Consistent with this, Nakagawa *et al.* (2002) found that in middle-aged individuals with intellectual disabilities, the MMN was considerably attenuated in amplitude, related to that in controls, in response to a small tone-frequency change. Ikeda *et al.* (2004) found an MMN deficit for tone-frequency and vowel changes in young adults with intellectual disability.

In patients with, or possible, Alzheimer's disease, the MMN is smaller in amplitude than that in age-matched controls (Pekkonen *et al.*, 1994; Kazmerski *et al.*, 1997; Gaeta *et al.*, 1999). This MMN deficit is dramatically increased when the stimulus-onset-asynchrony is prolonged (e.g. from 1 to 3 s; Pekkonen *et al.*, 1994), suggesting a pathologically shortened sensory-memory duration in Alzheimer's disease. Tales and Butler (2006) found a qualitatively and quantitatively abnormal visual MMN in Alzheimer's disease; for corroborating results, see Tales *et al.* (2008). Important for the prognostic perspectives, the mild cognitive impairment group showed a visual MMN data pattern resembling that of the patients with Alzheimer's disease (Tales and Butler 2006; Tales *et al.*, 2008) and, important for the therapeutic perspectives, Engeland *et al.* (2002) found that nicotinergic stimulation tended to normalize the amplitude and latency of the auditory MMN for tone-frequency change in patients with Alzheimer's disease.

Huntington's disease provides an interesting exception to the general rule that cognitive functions deteriorate globally in late

stages of various neurodegenerative disorders. Beste *et al.*, (2008) found that symptomatic patients with Huntington's disease performed better than presymptomatic gene-mutation carriers and controls in an auditory signal-detection task. These patients also had a larger MMN amplitude (above the right hemisphere) and shorter peak latency for tone-frequency change than those of controls and the presymptomatic subjects. The authors attributed this surprising result to an increased activity of the *N*-methyl-D-aspartate-receptor system, an assumed pathogenic mechanism in Huntington's disease, proposing that this increased activity might facilitate signal propagation at the striatal level. In other kinds of cognitive tasks, this data pattern was not replicated however; thus the authors concluded that improved functioning of specific cognitive processes can emerge together with deterioration of other cognitive functions in late stages of Huntington's disease.

Parkinson's disease

In patients with Parkinson's disease, the MMN for tone-frequency change was attenuated in amplitude (Pekkonen *et al.*, 1995). These patients also tend to show some cognitive impairment, at least at later stages of the disease (Parkinson's disease dementia; Rongve and Aarsland, 2006). Brønnick *et al.* (2010) found an MMN deficit for tone-frequency decrement in patients with Parkinson's disease who were also demented, whereas patients with no dementia showed normal-sized MMNs, as was previously shown by Karayanidis *et al.* (1995) for tone-duration decrement. Brønnick *et al.* (2010) proposed that the MMN attenuation in patients with Parkinson's disease is associated with the pathological processes leading to dementia in these patients and might be caused by subcortical serotonin depletion or a severe cholinergic deficit.

Down's syndrome

Down's syndrome is a congenital disorder caused by the presence of an extra 21st chromosome and it is almost always characterized by intellectual deficiency (Roizen and Patterson, 2003). Lalo *et al.* (2005) found that the MMN for a wide tone-frequency change was often absent in young adult patients (mean age 25 years) and, further, that when the MMN was present, it tended to be of a smaller amplitude and longer latency than that in the control group.

Neurodegenerative changes secondary to medical illness

In advanced stages of diabetes mellitus, some cognitive decline can often be observed (Helkala *et al.*, 1995). In a group of these patients, the MMN for tone-frequency change was attenuated in amplitude, and there was also a trend towards impaired performance in the Digit Span backward test (Vanhanen *et al.*, 1996). The authors estimated that the diabetic subjects of their study might have had a slight impairment of their verbal working memory.

In HIV infection, the later stages are usually accompanied by cognitive decline (Navia et al., 1990). In these patients, the MMN peak latency for a wide tone-frequency change was considerably prolonged with the declining immunological capacity (Schroeder et al., 1994). The authors concluded that the MMN peak latency may be a useful indicator of the progression of the disease, suitable for use in clinical practice and as a marker of therapeutic response to anti-viral or neuroprotective treatments.

Normal ageing

The MMN amplitude is systematically attenuated and its peak latency prolonged with ageing (Verleger et al., 1991; Schroeder et al., 1995; Pekkonen et al., 1996; Jääskeläinen et al., 1999; Gaeta et al., 2001, 2002; Bertoli et al., 2002; Ikeda et al., 2004; Kisley et al., 2005; Cooper et al., 2006; Horvath et al., 2007; Kiang et al., 2007, 2009; Schiff et al., 2008). A particularly convincing characterization of the MMN–age relationship was provided by Kiang et al. (2009), who carefully plotted MMN and P3a amplitudes for tone-duration increment across adulthood for 147 normal subjects and 253 patients with schizophrenia. Along with the MMN changes by age, the level of performance in different cognitive tasks was gradually decreased (Cansino, 2009). There is evidence linking these MMN changes to cognitive deterioration. For example, it was found by Kisley et al. (2005) that the MMN for an occasional stimulus-onset-asynchrony shortening was much smaller in amplitude in elderly (55–85 years) than young (18–23 years) subjects and, further, that in the elderly, the MMN was smaller in amplitude in those with weaker performance in a memory task and in the Tower of London task requiring a number of psychological processes attributed to the frontal cortex, including planning and working memory, than that in those with a better performance. In addition, Gaeta et al.'s (2001) elderly subjects (mean age 71.8 years) had an MMN for tone-frequency change with a smaller amplitude and longer latency than that in their young subjects (mean age 22.6 years). The elderly had poorer scores on neuropsychological tests of executive function than the young. In addition, the visual analogue of the auditory MMN was also attenuated with ageing (Tales et al., 2002; Tales and Butler, 2006).

There is an additional effect of ageing in the form of the shortening of the sensory–memory durations as estimated from the MMN-data pattern obtained by varying the stimulus-onset-asynchrony across the stimulus blocks (Pekkonen et al., 1996; Cooper et al., 2006). Interestingly, in the early years of life, there is a corresponding change of the memory-trace duration but in the opposite direction, of course (Glass et al., 2008a, b).

Altered states of consciousness

Sleep

With increasing drowsiness, the MMN tends to be attenuated; yet, an MMN with a low amplitude can usually be recorded in light sleep (Stages 1 and 2) (Paavilainen et al., 1987; Sallinen et al., 1994). Furthermore, the MMN is absent, or very small, at sleep stages III and IV, whereas it tends to reappear in rapid eye movement sleep (Sallinen et al., 1996; Atienza and Cantero, 2001; Atienza et al., 2002).

Sleep and rapid-eye movement sleep deprivation

Sleep deprivation results in performance decrement in a number of cognitive tasks. Zerouali et al. (2010) found that the MMN for frequency and duration changes was attenuated in amplitude by rapid eye movement sleep deprivation, which also decreases the level of cognitive performance. In addition, Raz et al. (2001) observed that the MMN for tone-frequency change was somewhat attenuated in amplitude at the end of a 36-h continuous sleep deprivation. By this time, there is also clear evidence of cognitive decline (Binks et al., 1999).

Coma

In patients in a comatose state, no MMN can usually be recorded unless a latent recovery process has started, leading to the return of consciousness and cognitive capacities in the near future. Therefore, the MMN can be used in coma-outcome prediction (Kane et al., 1993, 1996; Fischer et al., 1999, 2004, 2006a, b; Morlet et al., 2000; Fischer and Luaute, 2005; Luaute et al., 2005). Moreover, the MMN peak latency, measured at hospitalization, of survivors of coma caused by a severe head injury predicted, to some extent, their expressive language ability and visuo-spatial performance 1 year after the injury (Kane et al., 2000). Kotchoubey et al. (2003) showed that in using the MMN for the objective assessment of the remaining cognitive capacity, it is better to use complex rather than simple sound stimuli that may result in severe underestimation of the capacity. For a meta-analysis, see Daltrozzo et al. (2007).

Persistent vegetative state

Coma outcome can also be a compromise between life and death; the persistent vegetative state that may last for several months. The process of the recovery of consciousness and cognitive skills is accompanied by a dramatic MMN emergence while the unconscious patient crosses the borderline to consciousness (Wijnen et al., 2007). Furthermore, the MMN specifically reflects, and predicts, their cognitive status, as the MMN for tone-frequency change recorded at hospitalization predicted the level of consciousness and the extent of cognitive recovery even 2 years ahead (Wijnen et al., 2007). Van der Stelt and Boxtel (2008) proposed that the MMN may also have some diagnostic utility in differentiating vegetative states from the minimally conscious state (Zarza-Lucianez et al., 2007).

Drug effects supporting the mismatch negativity-cognition relationship

Above we have reviewed a large bulk of clinical evidence supporting the MMN-cognition relationship across a number of different diseases and abnormalities. We will now review psychopharmacological data pertinent to this issue. Javitt *et al.* (1996) proposed that in patients with schizophrenia, deficient *N*-methyl-D-aspartate-receptor function could explain MMN abnormalities, impaired auditory discrimination and cognitive dysfunction. This hypothesis received support from the authors' experiments in monkeys showing that the (intracortically recorded) MMN for tone-intensity decrement was abolished by MK-801 (a *N*-methyl-D-aspartate receptor antagonist) injection that left the afferent responses in layer 4 intact. Moreover, Tikhonravov *et al.* (2008) found that MK-801 attenuated the MMN amplitude for tone-frequency change in rats. Refer to Ehrlichman *et al.* (2008) for corroborating ketamine (an anaesthetic with *N*-methyl-D-aspartate-receptor antagonizing properties) results with the tone-frequency MMN recorded in mice. Consistent with this, in normal healthy human subjects, ketamine attenuated the MMN amplitude for tone-frequency and -duration changes (Umbricht *et al.*, 2000), prolonged the magnetoencephalographic MMN peak latency for frequency, duration and intensity changes and decreased the magnetoencephalographic MMN dipole moment, whereas it affected neither the N1m latency nor dipole moment (Kreitschmann-Andermahr *et al.*, 2001). Umbricht *et al.* (2002) found that normal healthy subjects with a smaller baseline MMN for tone-frequency changes (before any drug intake) were more affected (i.e. had a larger number of 'psychotic' responses on the Brief Psychiatric Rating Scale) by a small dose of ketamine than subjects with a larger MMN. An analogous pattern of results was obtained with duration changes. In a recent study by Lavoie *et al.* (2007), a 6-week administration of *N*-acetyl-cysteine, a glutathione precursor that can potentiate the activity of the *N*-methyl-D-aspartate receptors, corrected MMN deficiency for tone-frequency change in patients with schizophrenia, and there was also evidence for the improvement of the clinical condition (Berk *et al.*, 2008) [for further supportive evidence, see Coyle, 2006 and Schwieler *et al.* (2008)]. Importantly, this MMN recovery preceded clinical improvement and can thus serve as its predictor (Javitt, 2008, 2009). Horton *et al.* (2010) found that clozapine increased the MMN amplitude for tone-frequency changes, with increasing doses being associated with increasing frequency-MMN amplitudes (but with decreasing duration-MMN amplitudes).

In contrast, cognitive performance is adversely affected by alcohol, which also attenuated the MMN amplitude for tone-frequency change (Jääskeläinen *et al.*, 1996). Consistent with this, Pang and Fowler (1999) found that inhaling nitrous oxide (N₂O) attenuated the MMN amplitude for tone-frequency change, which even in sub-anaesthetic doses produces amnaesia and also has other adverse effects on cognition (Fowler *et al.*, 1985). Nakagome *et al.* (1998) found MMN-amplitude reduction for tone-frequency change on the morning following nocturnal triazolam administration, a short-acting benzodiazepine hypnotic also affecting cognitive function (Clark *et al.*, 1979). Serra *et al.* (1996) observed that the H1-receptor antagonist chlorpheniramine, known to impair cognitive performance (Nicholson *et al.*, 1991), attenuated the MMN amplitude for frequency change of a tone.

In contrast, nicotine has well-known cognition-enhancing effects. Such effects have been found in aged rodents, both in healthy smokers and non-smokers (Martin *et al.*, 2009), and in patients with schizophrenia (Inami *et al.*, 2007). Transdermal administration of nicotine shortened the MMN peak latency (Inami *et al.*, 2005) and oral administration of nicotine increased the MMN amplitude for interval duration (Martin *et al.*, 2009) and tone duration deviation (Baldeweg *et al.*, 2006) in normal healthy subjects. For consistent results with a consonant-vowel syllable change MMN, see Harkrider and Hendrick (2005). Also, the MMN for tone-frequency change was enhanced in amplitude and its peak latency shortened after the administration of the selective neuronal nicotinic receptor agonist AZD3480 in healthy volunteers (Dunbar *et al.*, 2007). Furthermore, Fisher *et al.* (2010) found that nicotine enhanced the visual MMN amplitude for change of the length of a vertically oriented bar and increased the amplitude of the auditory MMN for frequency change of a tone in normal healthy subjects.

In addition, Inami *et al.* (2007) reported that nicotine shortened the MMN peak latency for tone-frequency change in healthy control subjects, but not in non-smoking patients with schizophrenia. The authors attributed the weak MMN response to nicotine administration in non-smoking patients to low nicotinic receptor function implicated in the dysregulation of the glutamatergic system in these patients. In contrast, in patients with Alzheimer's disease, in whom nicotine has favourable effects on cognition, nicotine shortened the MMN peak latency and increased the MMN amplitude for tone-frequency change (Engeland *et al.*, 2002).

Mismatch negativity–cognition relationship in normal healthy populations

Even in the normal healthy population, the MMN seems to index cognition. Dividing their subjects into high-ability and low-ability groups on the basis of a comprehensive psychometric assessment, Bazana and Stelmack (2002) found that the MMN peak latency for frequency change in a backward-masking paradigm was considerably longer in the low- than high-ability group. Moreover, the MMN peak latency exhibited a substantial factor loading on the general (*g*) factor of intelligence in the battery of ability tests used. Subsequently, these results were corroborated and extended by Beauchamp and Stelmack (2006). In a similar vein, larger amplitude MMNs for syllable change were recorded in children with higher than lower level of general intellectual functioning by Liu *et al.* (2007).

Corroborating results were also obtained by Light *et al.* (2007). Their MMN data pattern for tone-duration increment in healthy

control subjects paralleled that previously obtained in patients with schizophrenia (Light and Braff, 2005a, b) in both the strength of the MMN-cognition association and the frontocentral scalp distribution. This equivalence of associations across groups and studies is, according to the authors, striking, because these healthy, non-psychiatric subjects performed within the normal range on all of the functional and cognitive measures, yet exhibiting enough range to reveal robust associations among disparate measures (i.e. MMN, cognitive and functional). These data indicate that sensory-level CNS information processing (as reflected by the MMN to auditory change) in clinically healthy individuals is strongly associated with cognitive and real-world psychosocial functioning of these individuals (Light et al., 2007).

Concluding discussion

The present review has shown that MMN abnormality is closely associated with cognitive change and decline occurring in a number of different neurological and neuropsychiatric illnesses as well as in normal ageing. Consequently, deficient auditory discrimination, as indexed by MMN (magnetoencephalographic MMN) deficiency, provides a convenient metric of this cognitive decline. Furthermore, it might even have a role in the aetiology of these cognitive deficiencies; deficient auditory discrimination might form an obstacle in particular to the linguistic development of the individual, starting even from the earliest stages of speech development (Kraus et al., 1996; Benasich et al., 2006; van Leeuwen et al., 2006; for a review see Kujala, 2007). Importantly, this temporofrontal cortex functional deficiency might also index a more general functional deficiency, such as the deficient neuromodulatory status (e.g. N-methyl-D-aspartate-receptor function) of the brain that would not be confined to the neural mechanisms of auditory discrimination but rather involves the whole cortex (Breier et al., 1997; Kohlmetz et al., 2001), hence affecting cognitive performance more generally, in different kinds of cognitive tasks. A N-methyl-D-aspartate-receptor dysfunction can affect cognition in many different ways. It is, for instance, well-established that the adequate functioning of this receptor system plays a crucial role in the initiation of long-term memory and probably also in that of working memory (Javitt et al., 1996; Newcomer et al., 1998) and in plastic changes in the brain in general (Izquidero, 1999; Santini et al., 2001; Gu et al., 2002; Siegel et al., 2003; Stephan et al., 2006; Heekeren et al., 2008; Izquidero, 1999). We have reviewed evidence for the central role of the N-methyl-D-aspartate-receptor dysfunction in the brain pathology of schizophrenia and, in particular, in the cognitive deficit in these patients (Olney and Farber, 1995; Coyle, 2006). We have also reviewed converging evidence showing that the administration of a glutathione precursor that can potentiate the N-methyl-D-aspartate receptor activity alleviated the MMN deficiency in patients with schizophrenia and subsequently also resulted in some clinical improvement in the state of patients (Lavoie et al., 2007). Moreover, the cognitive decline occurring in several other neurocognitive abnormalities might also be explained, at least in part, with the dysfunctional N-methyl-D-aspartate-receptor system. Alzheimer's disease, stroke, traumatic brain injury, and even normal ageing are accompanied by widespread dysfunctions in the N-methyl-D-aspartate-receptor system of the brain (Izquierdo 1991; Dalkara et al., 1996; Biegon et al., 2004; Magnusson et al., 2010; McGeer and McGeer, 2010; see also Bickel et al., 2008). For example, middle cerebral artery occlusion in rat resulted in widespread decreases in N-methyl-D-aspartate-receptor density in brain regions extending far beyond the infarct area, even including regions contralateral to the lesion important to cognitive function (Dhawan et al., 2010). Dhawan et al. (2010) therefore concluded that a persistent and widespread loss of these receptors may contribute to cognitive and other neurological deficits in stroke patients, which cannot be localized to the side of infarction.

Furthermore, it is also possible that the favourable effects of music and speech stimulation on cognitive performance and the magnetoencephalographic MMN found by Särkämö et al. (2010) in stroke patients in the early post-stroke period were mediated by improved glutamatergic transmission, involving the N-methyl-D-aspartate receptors. The authors suggested that glutamate may be a crucial neural factor linking auditory stimulation to changes in the magnetoencephalographic MMN, memory and stroke recovery.

Importantly, the association of the MMN with cognition is also supported by the fact that even the MMN generator itself is capable of performing complex cognitive processes (Näätänen et al., 2001, 2010). A number of recent MMN studies indicate that in audition, surprisingly complex processes occur automatically and mainly in the sensory-specific cortical regions. These processes include, e.g. stimulus anticipation and extrapolation (Tervaniemi et al., 1994; Winkler et al., 2009a; Todd et al., 2010), sequential stimulus-rule extraction (Zachau et al., 2005; Bendixen et al., 2007, 2008, 2009; Grimm and Schröger, 2007; Paavilainen et al., 2007; Schröger et al., 2007; Bendixen and Schröger, 2008; Sculthorpe et al., 2009; Winkler et al., 2009), and pattern and pitch-interval encoding (Stefanics et al., 2009; Winkler, Haden et al., 2009). Furthermore, these complex perceptual-cognitive processes, first found in waking adults (Saarinen et al., 1992), occur similarly even in sleeping newborns (Carral et al., 2005; Winkler et al., 2009b), anaesthetized rats (Astikainen et al., 2006; Ruusuvirta et al., 2007), and deeply sedated adult humans (Heinke and Koelsch, 2005), suggesting that they form the common perceptual-cognitive core of cognitive processes shared by different species, ontological stages, and states of consciousness (Näätänen et al., 2010). Consequently, these studies suggest that it might be possible to use the MMN in the objective assessment of cognitive abilities by recording it in paradigms targeting complex sensory-cognitive processes performed by sensory-specific-frontal cortical networks of the type reviewed above. This might complement the objective assessment of cognitive abilities already demonstrated by previously reviewed studies (Bazana and Stelmack, 2002; Beauchamp and Stelmack, 2006; Lin et al., 2007) recording the MMN for simple auditory changes.

Some other uses of the MMN and magnetoencephalographic MMN in clinical settings are the objective determination of (i) auditory discrimination accuracy for any auditory attribute (including speech sounds); (ii) sensory–memory duration (a possible index of general brain plasticity (Näätänen and Kreegipuu, 2010). This sensory-memory duration is gradually shortened in ageing

Table 1 MMN deficit indexes cognitive decline in neuropsychiatric and neurological disorders

Neuropsychiatric disorders
   Schizophrenia
   Chronic alcoholism
Neurological and neurodegenerative diseases
   Stroke
   Aphasia
   Velo-cardio-facial (DiGeorge) syndrome
   Multiple sclerosis
   Epilepsy
   Dementia
   Alzheimer's disease
   Intellectual disability
   Mild cognitive impairment
   Down's syndrome
   Parkinson's disease
   Coma (MMN predicting cognitive recovery)
   Persistent vegetative state (MMN predicting cognitive recovery)
   Huntington's disease (MMN and cognition are enhanced in parallel in the late, symptomatic stage of illness)
Other
   Ageing
   Sleep
   Sleep deprivation
   Rapid eye movement sleep deprivation
   Acute alcohol intoxication
   Other cognition-reducing drugs (e.g. benzodiazepines, nitrous oxide, ketamine, chlorpheniramine)
   Sedation and anaesthesia
   Diabetes mellitus (advanced stage)
   HIV

(Pekkonen *et al.*, 1996; Cooper *et al.*, 2006), chronic alcoholism (Polo *et al.*, 1999; Grau *et al.*, 2001), and in particular in Alzheimer's disease (Pekkonen *et al.*, 1994); (iii) auditory backward masking [abnormally strong in chronic alcoholism (Ahveninen *et al.*, 1999) and dyslexia (Kujala *et al.*, 2003)]; (iv) in addition, the MMN can be used in the monitoring of the patient's state [e.g. in coma (Fischer *et al.*, 1999), persistent vegetative state (Wijnen *et al.*, 2007), schizophrenia (Umbricht and Krljes, 2005), post-stroke recovery (Ilvonen *et al.*, 2003; Särkämö *et al.*, 2010)]; and (v) as a prognostic tool. For example, the MMN recorded in comatose patients strongly predicts the recovery of consciousness in the near future (Fischer *et al.*, 2004, 2006*a, b*; Fischer and Luaute, 2005). The MMN recorded in patients in persistent vegetative state predicted the extent of cognitive recovery during the period of the next 2 years (Wijnen *et al.*, 2007). In schizophrenia, the MMN predicts changes in the patient's state (Umbricht *et al.*, 2006; Kawakubo *et al.*, 2007), and even drug-treatment efficacy (Schall *et al.*, 1998; Lavoie *et al.*, 2007; Javitt *et al.*, 2008; Horton *et al.*, 2011). Most remarkably, the duration MMN predicts psychosis onset within 2 years and even the remaining lag time to conversion (Bodatsch *et al.*, 2011); and (vi) the MMN can also index genetic disposition to certain disorders such as schizophrenia (Jessen *et al.*, 2011; Michie *et al.*, 2002; Baker *et al.*, 2005; Hall *et al.*, 2007, 2009) and dyslexia (van der Leeuwen *et al.*, 2006).

In summary, the present review has shown that (i) cognitive decline is a core element shared by a large number of different neurological and neuropsychiatric illnesses as well as normal ageing; (ii) this cognitive decline is indexed by auditory-frontal-cortex dysfunction manifested in the form of compromised auditory discrimination or abnormally short sensory–memory traces; (iii) this auditory dysfunction can be objectively measured by using the MMN and its magnetic equivalent magnetoencephalographic MMN; (iv) the abnormality of these responses does not, however, express only a deficient local function but rather serves as a convenient index of a more widespread disorder in the brain such as deficient *N*-methyl-D-aspartate-receptor function; (v) these responses can therefore also index cognition and its decrement in ageing and in different neurological and neuropsychiatric abnormalities (Table 1); (vi) this conclusion is further supported by studies showing that pharmacological manipulations enhancing cognition also enhance the MMN (magnetoencephalographic MMN) response and vice versa, and further, that (vii) the MMN-cognition relationship holds even in normal populations.

In more general terms, the present review, aimed at contributing to the ongoing discussion on the similarities and differences between the different neurological and neuropsychiatric illnesses and abnormalities (e.g. Reite *et al.*, 2009; Hugdahl and Calhoun, 2010), indicates that cognitive decline in these disorders shows similarities in that it is associated with deficient low-level sensory processing. Irrespective of the very different aetiologies and symptomatologies, this deficiency is similarly reflected by a central auditory-system dysfunction, expressed by deficient neural

discrimination or shortened sensory-memory duration in audition indexed by MMN (magnetoencephalographic MMN) deficit. Future studies should therefore determine in detail the profiles of cognitive deterioration across the different types of cognitive performances separately for the different neuropsychiatric abnormalities. This would further clarify similarities of/differences between the different abnormalities and thus further confine the 'common nucleus' of cognitive decline shared by a large number of neuropsychiatric illnesses and abnormalities, as well as normal ageing.

Future studies should also determine whether the visual MMN is similarly useful as the auditory MMN in clinical research and settings (even though its reliable measurement in patients is much more demanding than that of the auditory MMN). It is possible that sensory-memory or context-related sensory processing (and its possible deficiencies) are quite similar across the different sensory modalities.

Reite *et al.* (2009) showed, as already mentioned, the presence of auditory-cortex structural and functional abnormalities in bipolar disorder and suggested that they might be due to altered neuronal migration patterns, genetic, epigenetic or both. According to the authors, recent findings in molecular cytogenetics concerning the role of altered DISC-1 proteins as they may impact neuronal migration might be considered in this regard. These proteins are involved in neuronal migration, synaptogenesis and glutamatergic, and GABAergic transmission (Bellon, 2007), and according to Reite *et al.* (2009), they appear to co-segregate with psychotic disorders as well as declined cognition, which supports a common pathophysiology contributing to a possible schizophrenia–schizoaffective disorder–bipolar continuum. Reite *et al.* (2009), however, concluded that magnetoencephalographic studies have not yet provided a neurophysiological measure of this common pathology. Fortunately, now it appears that this missing metric is provided by the MMN and its magnetoencephalographic equivalent, magnetoencephalographic MMN, an objective index of cognitive decline shared by a large number of different neurological and neuropsychiatric diseases and abnormalities, as well as by normal ageing.

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