The mismatch negativity (MMN) – A unique window to disturbed central auditory processing in ageing and different clinical conditions

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HIGHLIGHTS
• The mismatch negativity (MMN) indexes different types of central auditory abnormalities in different neuropsychiatric, neurological, and neurodevelopmental disorders.
• The diminished amplitude/prolonged peak latency observed in patients usually indexes decreased auditory discrimination.
• An MMN deficit may also index cognitive and functional decline shared by different disorders irrespective of their specific aetiology and symptomatology.
• MMN deficits index deficient N-methyl-D-aspartate (NMDA) receptor function affecting memory-trace formation and hence cognition in different disorders.

ABSTRACT
In this article, we review clinical research using the mismatch negativity (MMN), a change-detection response of the brain elicited even in the absence of attention or behavioural task. In these studies, the MMN was usually elicited by employing occasional frequency, duration or speech-sound changes in repetitive background stimulation while the patient was reading or watching videos. It was found that in a large number of different neuropsychiatric, neurological and neurodevelopmental disorders, as well as in normal ageing, the MMN amplitude was attenuated and peak latency prolonged.

Besides indexing decreased discrimination accuracy, these effects may also reflect, depending on the specific stimulus paradigm used, decreased sensory-memory duration, abnormal perception or attention control or, most importantly, cognitive decline. In fact, MMN deficiency appears to index cognitive decline irrespective of the specific symptomologies and aetiologies of the different disorders involved.

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Contents
1. Introduction ......................................................................................................... 425
2. The MMN as an index of decreased auditory discrimination accuracy (Table 1) ................................................... 431
3. The MMN as an index of shortened sensory-memory duration (Table 2) ........................................................ 433

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1. Introduction

Interestingly, central auditory processing is affected in a large number of different clinical conditions with very different aetiologies and symptoms such as schizophrenia, dyslexia, stroke, specific language impairment (SLI), multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), epilepsy and autism, suggesting some shared aetiology in these different abnormalities (see also Gottesman and Gould, 2003; Bishop, 2009; Dolan et al., 1993; Hugdahl and Calhoun, 2010; Reite et al., 2009). These effects on central auditory processing in different clinical conditions and in ageing can now be objectively evaluated, and hence their degree of similarity determined, by using the electrophysiological change-detection (or regularity-violation) response, the mismatch negativity (MMN; Näätänen et al., 1978; Näätänen and Michie, 1979) and its magnetoencephalographic (MEG) equivalent, the MMNm (Hari et al., 1984; Sams et al., 1985b). The MMN can be reliably (Pekkonen et al., 1995a,b; Escera and Grau, 1996; Tervaniemi et al., 1999; Escera et al., 2000b) recorded even in the absence of the subject or patient’s attention or behavioural task, e.g., in sleeping infants (Ruusuvirta et al., 2009), stroke patients even at a very early post-stroke-onset period (Ilvonen et al., 2001, 2004) and in comatose (Kane et al., 1993, 1996; Fischer et al., 1999; Fischer and Luauté, 2005) and persistent-vegetative-state (PVS) patients (Wijnen et al., 2005).

Fig. 1. Grand average difference waveforms (9 subjects) for changes in duration, frequency, and perceived sound-source location for six different magnitudes of deviance at electrode Fz and referenced to the mean of the two mastoid electrodes (upper panel). The same waveforms referenced to the nose electrode and shown from Fz and the right mastoid (RM); lower panel. Sound onset is always at 0 ms (From Pakarinen et al., 2007).
The auditory MMN response is mainly generated by a change-detection process occurring bilaterally in auditory cortices, in which the current auditory input is found to differ from the representation of the preceding auditory events, including regularities governing consecutive stimulus events (for reviews, see Näätänen et al., 2001, 2007, 2010, 2011b; Duncan et al., 2009; Winkler, 2007). For an illustration, see Fig. 1. In subjects performing some primary, e.g., visual, task, this preconscious auditory-cortex change-detection process reaches conscious perception by activating, with a brief delay (Rinne et al., 2000; see also Rinne et al., 2005, 2006), a right frontal-cortex process which, in turn, initiates further cerebral processes which may lead to conscious change detection (Näätänen, 1990, 1992; Näätänen et al., 2011b; Alain et al., 1998; Berti and Schröger, 2001; Deouell et al., 2007; Giard et al., 1990; Schröger, 1996; Escera et al., 2000a). Hence, the MMN is composed of overlapping contributions from auditory- and frontal-cortex processes (the supratemporal and frontal MMN subcomponents, respectively) (Giard et al., 1990). These two subcomponents of the MMN can be inferred from the data presented in Fig. 2 showing how ethanol selectively attenuates the MMN amplitude recorded over the frontal cortex, whereas the polarity-reversed MMN recorded at the mastoids (with a nose reference) is unaffected. This data pattern suggests that the frontally recorded MMN is composed of contributions from both the auditory and frontal cortices, whereas the mastoid ‘MMN’ gets a contribution from the auditory-cortex MMN generator only. Intracranial recordings in humans also support both auditory- and frontal-cortex MMN generators (Halgren et al., 1995a,b, 1998; Baudena et al., 1995; Kropotov et al., 1995, 2000; Liiasis et al., 1999, 2000a,b; Rosburg et al., 2005, 2007).

The MMNm, in turn, selectively reflects the temporal-lobe component of the MMN because the MEG is insensitive to the radially oriented frontal generators (Hämäläinen et al., 1993) of the MMN. Therefore, the MMNm is particularly well suited for detecting central auditory processing deficits specific for the temporal lobes. Consequently, the combined use of the electroencephalography (EEG) and MEG recordings helps one to separately determine to what extent the temporal and frontal MMN components are impaired (Hämäläinen et al., 1993; Näätänen, 1992). Further, these two components have their functional magnetic resonance imaging (fMRI) ( Molholm et al., 2005; Celsis et al., 1999; Opitz et al., 2002; Schall et al., 2003 ), positron emission tomography (PET) (Tervaniemi et al., 2000; Dittmann-Balcar et al., 2001; Müller et al., 2002) and optical-imaging (OI) (Rinne et al., 1999; Tse and Penney, 2008 ) equivalents as well. Moreover, there is event-related potential (ERP; Paavilainen et al., 1991; Doeller et al., 2003; Frodl-Bauch et al., 1997; Escera et al., 2002), MEG ( Levänen et al., 1993, 1996; Rosburg, 2003 ) and fMRI evidence ( Molholm et al., 2005 ) for the attribute-specific organisation of the supratemporal MMN generator.

Moreover, the MMN has its equivalents in other sensory modalities, too [the visual MMN; vMMN ( Alho et al., 1992; Amenedo et al., 2007; Astikainen and Hietanen, 2009; Tales et al., 1999, 2002a,b, 2008; Tales and Butler, 2006; Maekawa et al., 2005, 2009; Berti and Schröger, 2004, 2006; Stagg et al., 2004; Stefanics et al., 2011; Heslenfeld, 2003; Pazó-Alvarez et al., 2003, 2004; Froyen et al., 2010; Iijima et al., 1996; Kenemans et al., 2003; Kimura et al., 2009; Czigler, 2007; Czigler and Csibra, 1990, 1992; Czigler et al., 2002, 2004, 2006a,b; Czigler and Pató, 2009; Nordby et al., 1996; Wei et al., 2002; Woods et al., 1992); the somatosensory MMN; sMMN (Kekoni et al., 1997; Shinozaki et al., 1998; Akatsuka et al., 2005; Kida et al., 2001; Spackman et al., 2007, 2010; Astikainen et al., 2001; Näätänen, 2005); and the olfactory MMN; oMMN (Krauel et al., 1999; Pause and Krauel, 2000)]. The vMMN has a parieto-occipital scalp distribution but there is no convincing evidence for a frontal component analogous to that in the auditory modality. By contrast, the sMMN appears to have, similar to the auditory MMN, sensory-specific (somatosensory cortex) and frontal subcomponents ( Restuccia et al., 2009; Spackman et al., 2010), consistent with its fronto-central, contralaterally predominant scalp distribution (Wei et al., 2002). Currently, it is not clear whether the auditory and somatosensory modalities share the frontal activation (generating the frontal MMN component) probably serving attention switch to stimulus change (Näätänen, 1992; Näätänen et al., 2002; Schröger, 1997 ). In addition, there is also an oMMN, with a long peak latency (about 500–600 ms) and parietally predominant scalp distribution (Krauel et al., 1999).

The MMN can also be recorded in different animals [in monkey (Javitt et al., 1992); cat ( Csépe et al., 1987, 1988, 1989; Pinzce et al., 2001, 2002); rabbit (Astikainen et al., 2001); rat (Astikainen et al., 2006; Ruusuvirta et al., 1998, 2007; Roger et al., 2009; Tikhonravov et al., 2008, 2010); guinea pig (Kraus et al., 1994); and mouse (Umbricht et al., 2005; Ehrlrich et al., 2008, 2009)]. The MMN enables one to determine discrimination accuracy, usually with a good correspondence with behavioural discrimination (Sams et al., 1985a; Amenedo and Escera, 2000; Gottselig et al., 2004; Lang et al., 1990; Näätänen et al., 1993, 2007; Leitman et al., 2010; Kujala and Näätänen, 2010; Tremblay et al., 1998), separately for each auditory dimension (such as frequency, intensity and duration) as well as for the different speech sounds (Kraus et al., 1996), with the MMN vanishing at about the behavioural discrimination threshold (Sams et al., 1985a; Winkler and Näätänen, 1994; Winkler et al., 1993). Therefore, it permits one to form objective deterioration profiles covering all important auditory dimensions in different patient groups (Näätänen et al., 2004; Kujala et al., 2005a, 2006, 2007, 2010; Pakarinen et al., 2007, 2009, 2010). In addition, these MMN-based objective tests can be extended to all aspects of short-term auditory sensory memory, too, such as its...
Table 1
The auditory MMN (MMNm) provides an objective index of affected auditory discrimination in:

- **ADHD** (Alexandrov et al., 2003; Barry et al., 2003; Gumenyuk et al., 2005; Huttunen et al., 2007; Huttunen-Scott et al., 2008; Kenner et al., 1996; Kilpeläinen et al., 1999; Oades et al., 1996; Rothenberger, 1995; Rothenberger et al., 2000; Satterfield et al., 1988; Sawada et al., 2010; Wild-Wall et al., 2005; Winsberg et al., 1993)
- **Ageing** (Alain and Woods, 1999; Alain et al., 2004; Amenedo and Diaz, 1998; Bellis et al., 2000; Bertoli et al., 2005; Cooper et al., 2006; Czigler et al., 1992; Fabiani et al., 2006; Gaeta et al., 1998, 1999, 2001, 2002; Gunter et al., 1996; Horváth et al., 2007; Iijima et al., 1996; Ikeda et al., 2004; Jääskeläinen et al., 1999a; Karayanidis et al., 1995; Kiang et al., 2006, 2009; Kisley et al., 2004a,b, 2005; Kok, 2000; Mager et al., 2005; Osawa et al., 1996; Pekkonen, 2000; Pekkonen et al., 1994, 1995, 1996a, 1999, 2001a,b; Riekkinen et al., 1997; Schroeder et al., 1995; Yokoyama et al., 1995)
- **Alcohol intoxication, acute** (Ahveninen et al., 2000a,b; Fein et al., 2004; Grau et al., 2001; Holguin et al., 1998; Kathmann et al., 1995; Marco-Pallares et al., 2007; Pekkonen et al., 1998; Polo et al., 2003; Realmuto et al., 1993; Rodriguez et al., 1993, 1994; van der Stelt and Belger, 2007; Zhang et al., 2001)
- **Alzheimer’s disease and dementia** (Engeland et al., 2002; Gaeta et al., 1999; Katada et al., 2004; Kazmerski et al., 1997; Missioner et al., 1999; Pekkonen, 2000; Pekkonen et al., 1994, 1995, 1996b, 1999, 2001a,b; Riekkinen et al., 1997; Schroeder et al., 1995; Yokoyama et al., 1995)
- **Amusia (Congenital)** (Moreau et al., 2009; Peretz et al., 2009)
- **Amusia (Caused by Stroke)** (Kohlmetz et al., 2001; Särkämö et al., 2010b)
- **Amyotrophic Lateral Schlerosis (ALS)** (Gil et al., 1993; Hanagasi et al., 2002; Pekkonen et al., 2004; Raggi et al., 2008)
- **Anaesthesis and sedation** (Csepe et al., 1989; Heinke and Koelsch, 2005; Heinke et al., 2004; Korpilahti et al., 2006; Yppärilä et al., 2002; Simpson et al., 2002; van Hooff et al., 1995, 1997)
- **Anhedonia** (Giese-Davis et al., 1993)
- **Aphasia and stroke** (Aaltonen et al., 1993; Alain et al., 1998; Auer et al., 2000; Becker and Reinvang, 2007; Csépe et al., 2001; Ivonen et al., 2003, 2004; Jacobs and Schneider, 2003; Kohlmetz et al., 2001; Peach et al., 1992, 1993, 1994; Pettigrew et al., 2004a, 2005; Särkämö et al., 2010a,b; Wertz et al., 1998)
- **Asperger syndrome** (Jansson-Verkasalo et al., 2003a, 2005; Korpilahti, 1995; Korpilahti et al., 2007; Kujala et al., 2005a, 2007, 2010; Lepistö et al., 2005, 2006, 2007)
- **Autism** (Bomba and Pang, 2004; Cepioniene et al., 2003; Dunn et al., 2008; Ferri et al., 2003; Comot et al., 2002; Kasai et al., 2005; Kenner et al., 1995; Kuhl et al., 2005; Lepistö et al., 2005, 2008; Näätänen and Kujala, 2011; Oram Cardy et al., 2005a,b; Roberts et al., 2008, 2011; Seri et al., 1999, 2007; Siegal and Blades, 2003)
- **Bipolar disorder** (Hall et al., 2007, 2009; Takei et al., 2010)
- **Bipolar II disorder** (Andersson et al., 2008)
- **Brain lesions** (Alain et al., 1998; Alho et al., 1994; Auer et al., 2000; Deouell et al., 2000a,b; Hamalainen et al., 2007; Jacobs and Schneider, 2003; Kaipio et al., 1999, 2000, 2001; Kohlmetz et al., 2001; Kotchoubey, 2007; Kotchoubey et al., 2003, 2005; Mäkelä et al., 1998b; Neumann and Kotchoubey, 2004; Polo et al., 2002; Reinvang et al., 2000; Tarkka et al., 2011; Woods and Knight, 1986); (see also Aphasia and Stroke)
- **Brainstem auditory processing syndrome** (Kraus et al., 1993a)
- **CATCH-22 syndrome** (Baker et al., 2005; Cheour et al., 1998a; Cepioniene et al., 2002)
- **Central auditory processing disorder (CAPD)** (Ramiou et al., 2000)
- **Cerebellar degeneration** (Moberget et al., 2008)
- **Childhood cancer and brain radiation** (Jarvelä et al., 2011; Lähteenmäki, 1999)
- **Chronic pain** (Dick et al., 2003)
- **Chronic primary insomnia** (Wang et al., 2001)
- **Cleft palate (different forms of)** (Cepioniene et al., 2000, 2002; Cheour et al., 1998a, 1999)
- **Closed-head injury** (Kaipio et al., 1999, 2000, 2001; Polo et al., 2002)
- **Cochlear-implant (CI) users** (Groenen et al., 1996; Kelly et al., 2005; Kileny et al., 1998; Koelsch et al., 2004; Kraus et al., 1993b; Lonka et al., 2004; Nager et al., 2007; Ponton et al., 1996, 2000, 2009; Ponton and Don, 1995, 2003; Ponton and Eggertmont, 2007; Roman et al., 2005; Salo et al., 2002; Sandmann et al., 2010; Wable et al., 2000)
- **Cona** (Daltrozzo et al., 2007; Fischer et al., 1999, 2000, 2004, 2006a,b, 2008; Fischer and Luauté, 2005; Guérin et al., 1999; Kane et al., 1993, 1996, 2000; Kotchoubey et al., 2003; Laureys et al., 2005; Luauté et al., 2005; Morlet et al., 2000; Naccache et al., 2005; van der Stelt and van Boxtel, 2008; Vanhaudenhuyse et al., 2008)
- **Conduct disorder** (Rothenberger et al., 2000)
- **Craniosynosthosis** (Huotilainen et al., 2008)
- **Deafness to musical dissonance (Acquired)** (Battico et al., 2003)
- **Dementia** (Rothenberger et al., 1995; Yokoyama et al., 1995; Osawa et al., 1996)
- **Depression** (He et al., 2010; Iv et al., 2010; Kähkönen et al., 2007; Lepistö et al., 2004; Ogura et al., 1991, 1993; Takei et al., 2009)

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<th>Table 1 (continued)</th>
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<tr>
<td><strong>– Developmental dysphasia</strong> (Holopainen et al., 1997, 1998; Korpihahti and Lang, 1994)</td>
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<td><strong>– Diabetes mellitus</strong> (late phase) (Vanhanen et al., 1996)</td>
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<td><strong>– Distractibility</strong> (Escera et al., 2000a; Gumenyuk et al., 2004; Kaipio et al., 2000, 2001; Kilpeläinen et al., 1999; Mager et al., 2005)</td>
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<tr>
<td><strong>– Down’s syndrome</strong> (Diaz and Zurron, 1995; Lalo et al., 2005)</td>
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<td><strong>– Drugs</strong></td>
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<td><strong>– Antipsychotics/Neuroleptics:</strong></td>
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<td>– Clozapine (Horton et al., 2010; Schall et al., 1999; Umbricht et al., 1998)</td>
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<td>– Haloperidol (Kähkönen and Ahveninen, 2002; Kähkönen et al., 2001, 2002; Pekkonen et al., 2002)</td>
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<td>– Olanzapine (Korostenskaja et al., 2005)</td>
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<td>– Risperidone (Umbricht et al., 1999)</td>
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<td>– Alcohol:</td>
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<td>– Acetylcholine:</td>
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<tr>
<td>Tetrahydroaminoacridine (THA, Tacrine) (Engeland et al., 2002; Riekkinen et al., 1997)</td>
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<td>(a) Muscarinic receptor antagonist:</td>
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<td>– Glycopyrrolate (Pekkonen et al., 2001a)</td>
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<td>– Scopolamine (Pekkonen et al., 2001a)</td>
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<td>(b) Nicotinic receptor agonists:</td>
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<td>– Nicotine: (Balíš et al., 2006; Dulude et al., 2010; Engeland et al., 2002; Fisher et al., 2010; Harkrider and Hedrick, 2005; Inami et al., 2005, 2007; Knott et al., 2009; Martin et al., 2009; Pritchard et al., 2004)</td>
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<td>– AZD3480 (Dunbar et al., 2007)</td>
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<td>– Benzodiazepines:</td>
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<td>– (Kivisaari et al., 2007; Murakami et al., 2002)</td>
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<td>– Triazolam (Nakagome et al., 1998)</td>
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<td>– Lorazepam (Rosburg et al., 2004)</td>
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<td>– GABA agonists/antagonists:</td>
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<td>– Bicuculline (Javitt et al., 1996)</td>
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<td>– Flumazenil (Smolnik et al., 1998)</td>
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<td>– Propofol (Heinke et al., 2004; Koelsch et al., 2006; Simpson et al., 2002)</td>
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<td>– Monoamines</td>
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<td>– Review: (Kähkönen and Ahveninen, 2002)</td>
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<td>– Adrenergic drugs:</td>
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<td>– Clonidine (Duncan and Kaye, 1987; Hansenne et al., 2003)</td>
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<td>– Atipamezole (Mervaala et al., 1993)</td>
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<td>– Noradrenergic agonist S 12024-4 (Missioner et al., 1999)</td>
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<td>– Histamine:</td>
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<td>– Antihistamines: Chlorpheniramine (Serra et al., 1996)</td>
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<td>– Dopamine:</td>
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<td>– Apomorphine (Hansenne et al., 2003)</td>
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<td>– Methamphetamine (Hosák et al., 2008)</td>
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<td>– Methylphenidate (Winsberg et al., 1993, 1997; Sawada et al., 2010; Verbaten et al., 1994)</td>
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<td>– Bromocriptine (Leung et al., 2007)</td>
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<td>– Dopemidone (Leung et al., 2007)</td>
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<td>– Serotonin:</td>
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<td>– Serotonin (Kähkönen et al., 2005a; Oranje et al., 2008)</td>
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<td>– Acute tryptophan depletion (Kähkönen and Ahveninen, 2002)</td>
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<td>– Dimethyltryptamine (Heekeren et al., 2008)</td>
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<td>– Escitalopram (Oranje et al., 2008; Wienberg et al., 2010)</td>
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<td>– Psilocybin (Umbricht et al., 2003)</td>
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<td>– Neuropeptides/Hormones:</td>
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<td>– Vasopressin (Born et al., 1986, 1987a, 1998)</td>
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<td>– Oxytocin (Born et al., 1987a)</td>
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<td>– Cholecystokinin (Schreiber et al., 1995)</td>
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<td>– Desacetyl-alpha-MSH (Smolnik et al., 1999)</td>
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- Hydrocortisone (Born et al., 1987a)
- ACTH-related neuropeptides (Born et al., 1987b; Smolnik et al., 1999; Pietrowsky et al., 1990)
- NMDA/Glutamate:
  - Ketamine (Ehrlichman et al., 2008; Heekeren et al., 2008; Javitt et al., 2000; Kreitschmann-Andermahr et al., 2001; Umbricht et al., 2002)
  - MK-801 (Javitt et al., 1996; Tikhonravov et al., 2010)
  - Phencyclidine (PCP) (Javitt et al., 1996)
  - Memantine (Korostenskaja et al., 2010b)
  - Nitrous oxide (Pang and Fowler, 1999)
  - Glycine (Leung et al., 2008)
- N-acetyl-cysteine (NAC; Lavoie et al., 2007)
- Opioids:
  - Naltrexone (Jääskeläinen et al., 1998)
  - Opioid Dependence (Kivisaari et al., 2007; Näätänen, 2001)
- Other/alternative therapies:
  - Hiba odour (Hiruma et al., 2002)
  - Purine nucleotides:
    - Adenosine (Hirvonen et al., 2000)
    - Caffeine (Rosburg et al., 2004)
  - Dysthymia (Giese-Davis et al., 1993)
  - Electromagnetic fields
    - (Kwon et al., 2009, 2010)
  - Epilepsy
    - (Boatman et al., 2008; Borghetti et al., 2007; Duman et al., 2008; Gene-Cos et al., 2005; Korostenskaja et al., 2010b; Liasis et al., 2000; Liasis et al., 2001; Liasis et al., 2006; Lin et al., 2007; Metz-Lutz and Philippini, 2006; Miyajima et al., 2011; Ragazzoni et al., 2000; Woods and Knight, 1986)
  - Frontal-lobe injury (Alho et al., 1994; Woods and Knight, 1986)
  - Herpes Simplex Encephalitis (Mäkelä et al., 1998a)
  - Hippocampus-Amygdala Partial Temporal-Lobe Resection (Hämäläinen et al., 2007)
  - HIV (Schoedro et al., 1994)
  - Huntington's disease (pathological enhancement of discrimination) (Beste et al., 2008)
  - Hyperkinetic disorder (Rothenberger, 1995)
  - Hypnosis (Jamierson et al., 2005; Kallio et al., 1999)
  - Inosiné (Wang et al., 2001)
  - Intellectual disability (Ikeda et al., 2004; Nakagawa et al., 2002; Kaga et al., 1999)
  - Introvert/extrovert personality (Sasaki et al., 2000)
  - Landau–Kleffner syndrome (Honbolgyó et al., 2006; Metz-Lutz and Philippini, 2006)
  - Language-learning impairment (LLI) (Benasich and Tallal, 2002; Benasich et al., 2006; Bradlow et al., 1999; Choudhury and Benasich, 2011; Kraus et al., 1996; Kujala, 2007; Marler et al., 2002; Pihko et al., 2007; Shafer et al., 2005; Uwer et al., 2002; Weber et al., 2005)
  - Late talkers (Grossheinrich et al., 2010)
  - Learning-disabled children (Banai and Ahissar, 2005; Bradlow et al., 1999; Kraus et al., 1996)
  - Left sylvian infarct in neonate (Dehaene-Lambertz et al., 2004)
  - Locked-in patients (Ragazzoni et al., 2000)
  - Meditation (Srinivasan and Basijal, 2007)
  - Mental work load (Kramer et al., 1995)
  - Mental retardation (Holopainen et al., 1998; Ikeda et al., 2004; Kaga et al., 1999; Nakagawa et al., 2002; Yokoyama et al., 1995; Zurrón and Diaz, 1997)
  - Migraine (de Tommaso et al., 2004; Korostenskaja et al., 2010a; Valeriani et al., 2008)
  - Multiple sclerosis (MS) (Gil et al., 1993; Jung et al., 2006; Santos et al., 2006)
  - Narcolepsy (Naumann et al., 2001)
  - Neglect (Fernfield inattention) and extinction (Deouell et al., 2000a,b; Tarakka et al., 2011)
  - Noise and distraction (Bertoli et al., 2005; Gumenyuk et al., 2004; Mikloa et al., 2010; Shyrov et al., 1998, 1999; Simoens et al., 2007)
  - Noise, different types of (Kozou et al., 2005)
  - Noise, occupational (Mántysalo and Salmin, 1989)
  - Noise, occupational, long-term exposure (Brattico et al., 2005; Kujala and Brattico, 2009; Kujala et al., 2004)
  - Obsessive–compulsive disorder (Towey et al., 1994; Oades et al., 1996)
  - Obstructive sleep apnea syndrome (OSAS) (Gosselin et al., 2006)
  - Opioid dependence (Kivisaari et al., 2007)
  - Parkinson's disease (Bannick et al., 2010; Karayanidis et al., 1995; Pekkonen et al., 1995c; Viereregger et al., 1994)
  - Perinatal asphyxia (Leipälä et al., 2011)

(continued on next page)
- Perinatal intracerebral hemorrhage (Leipälä et al., 2011)
- Persistent vegetative state (Boly et al., 2011; Fischer and Luauté, 2005; Kotchoubey, 2007; Kotchoubey et al., 2003, 2007, 2008; Laureys et al., 2005; Wijnen et al., 2007; Zarza-Lucianez et al., 2007)
- Personality differences (Matsubayashi et al., 2008; Franken et al., 2005)
- Phonological deficit (Blitz et al., 2007)
- Plagiocephaly (Huotilainen et al., 2008)
- Post-traumatic stress syndrome (PTSS) (Cornwell et al., 2007; Ge et al., 2011; Menning et al., 2008; Morgan and Grillon, 1999)
- Psychosocial stress (Simoens et al., 2007)
- Prematurely born (with very low birth weight, VLBW) infants (Bisiachi et al., 2009; Cheour-Luhtanen et al., 1996; Fellman and Huotilainen, 2006; Fellman et al., 2004; Gomot et al., 2007; Holst et al., 2005; Jansson-Verkasalo et al., 2004, 2010; Leipälä et al., 2011; Mento et al., 2010; Mikkola et al., 2007, 2010)
- REM-sleep deprivation (Zerouali et al., 2010)
- Schizophrenia (Ahveninen et al., 2006; Baldeweg et al., 2002, 2004; Banati and Hickie, 2009; Bodatsch et al., 2011; Braff and Light, 2004; Brockhaus-Dumke et al., 2005; Catts et al., 1995; Davalos et al., 2003, 2005; Devrim-Ucok et al., 2008; Ehrlichman et al., 2008, 2009; Fisher et al., 2008, 2011; Grzella et al., 2001; Hermens et al., 2010; Hirayasu et al., 1998, 2000, 2001; Inami et al., 2007; Jahshan et al., 2011; Javitt, 1993, 2000, 2009a,b; Javitt et al., 1996, 1998, 1999, 2000, 2008; Jessen et al., 2001; Kasai et al., 2001, 2002a,b,c; Kathmann et al., 1995; Kaur et al., 2011; Kawakubo et al., 2006, 2007; Kiang et al., 2007, 2009; Kircher et al., 2004; Korostenskaja et al., 2005; Kreitschmann-Andermahr et al., 1999, 2001; Lavoe et al., 2007; Leitman et al., 2010; Light and Braff, 2005a,b; Luck et al., 2011; Magno et al., 2008; Matthews et al., 2007; Michie, 2001; Michie et al., 2002; Minami and Kirino, 2005; Morlet et al., 2000; Näätänen and Kähkönen, 2009; Niznikiewicz et al., 2009; Oades et al., 2006; Oknina et al., 2005; Park et al., 2002; Potts et al., 1998; Price et al., 2006; Rasser et al., 2011; Risling et al., 2010; Salisbury et al., 2002, 2007; Sato et al., 1998, 2002; Schall et al., 1998, 1999, 2003; Schreiber et al., 1992; Shelley et al., 1991; Shin et al., 2009; Shinozaki et al., 2002; Stone et al., 2000, 2002, 2003, 2006; van der Stelt and Belger, 2007; Verbaten and van Engelund, 1995; Wible et al., 2001; Wynn et al., 2002; Yamase et al., 2004; Youn et al., 2003; for a meta-analysis of 32 studies, see Umbricht and Krijes, 2005)
- Serotonin transporter gene variants, individuals with (Sysoeva et al., 2009)
- Sensorineural hearing loss (Oates et al., 2002; Stapells, 2002)
- Sleep (Atienza et al., 1997, 2000, 2002; Atienza and Cantero, 2001; Campbell et al., 1991; Cheour et al. 2000, 2002; Martynova et al., 2003; Nashida et al., 2000; Nittono et al., 2001; Ruby et al., 2008; Sallinen et al., 1994, 1996; Sculthorpe et al., 2009)
- Sleep deprivation (Gumenyuk et al., 2010; Raz et al., 2001; Sallinen and Lytinen, 1997; Salmi et al., 2005; Wang et al., 2001; Zerouali et al., 2010)
- Socially withdrawn children (Bar-Haim et al., 2003)
- Somatisation disorder (James et al., 1989)
- Specific language impairment (SLI) (Barry et al., 2008; Bishop and McArthur, 2004; Friederich et al., 2004; Korpilahti, 1995; Marler et al., 2002; Pihko et al., 2008; Rinker et al., 2007; Shafer et al., 2007; Uwer and von Suchodoletz, 2000; Uwer et al., 2002; Weber et al., 2005)
- Stroke (see Aphasia)
- Stuttering (Corbera et al., 2005; Wu et al., 1997)
- Temporal-parietal brain lesions (Alain et al., 1998)
- Thalamic infarction (Makela et al., 1998b)
- Tourette syndrome (TS) (Oades et al., 1996; Rothenberger et al., 2000; van Woerkom et al., 1988, 1994)
- Tune deafness (Braun et al., 2008)
- Velo-cardio-facial (DiGeorge) syndrome (Baker et al., 2005)
duration, capacity and accuracy (Pekkonen et al., 1996a; Cooper et al., 2006; Polo et al., 1999; Grau et al., 2001). Furthermore, the auditory MMN can even index auditory long-term memory traces such as the language-specific memory traces, enabling one to correctly perceive the speech sounds of the mother tongue and other such as the language-specific memory traces, enabling one to correctly perceive the speech sounds of the mother tongue and other familiar languages (Dehaene-Lambertz, 1997; Näätänen, 2001; Näätänen et al., 1997; Pulvermüller et al., 2004; Shtryov and Pulvermüller, 2007). This linguistic MMN subcomponent is usually left-hemispherically predominant and generated posteriorly to the bilateral MMN subcomponent for mere acoustic change (Näätänen et al., 1997; Shestakova et al., 2002).

The extensive MMN literature of clinical studies can be classified according to the kind of clinically useful information that can be obtained by using the MMN. The MMN can index:

(1) Auditory discrimination accuracy (which is decreased in a number of clinical groups and affected by different drugs) (Table 1);
(2) shortened sensory-memory duration (and hence possibly decreased general brain plasticity) (Table 2);
(3) abnormal auditory perception;
(4) increased backward masking (Table 3);
(5) abnormal involuntary attention switching, either too weak (Table 4) or too strong (Table 5);
(6) cerebral grey-matter loss and other structural changes (Table 6);
(7) pathological brain excitation/excitability state (Table 7);
(8) cognitive and functional decline (Table 8);
(9) the level of consciousness (Table 9);
(10) the progression of illness (Table 10);
(11) future clinical condition (prognosis) (Table 11);
(12) genetic disposition to certain disorders (Table 12); and
(13) recovery/improvement as a function of time or treatment (Table 13).

Moreover, recent studies using the vMMN (Iijima et al., 1999; Lorenzo-Lopez et al., 2004; Tales and Butler, 2006; Tales et al., 2002a,b; Kenemans et al., 2010; Tales and Butler, 2006; Tales et al., 2002a, 2008; Maekawa et al., 2011; Froyen et al., 2010; Chang et al., 2010; Qiu et al., 2011; Horimoto et al., 2002; Hosák et al., 2008; Kremláček et al., 2008, Verbaten et al., 1994; Tales and Butler, 2006; Tales et al., 2008; Fisher et al., 2010; Urban et al., 2008; for a recent review, see Kimura et al., 2011) and sMMN (Restuccia et al., 2007; Akatsuka et al., 2005, 2007; Näätänen, 2009) have also provided clinically important results.

The present review aims at covering all clinical MMN studies in the auditory modality published in refereed international English-language journals. Almost all these studies report, with only a few exceptions, group-level results.

2. The MMN as an index of decreased auditory discrimination accuracy (Table 1)

In several clinical conditions, the MMN amplitude is attenuated, usually indexing decreased behavioural discrimination accuracy (Javitt et al., 1998; Rabinowicz et al., 2000; Matthews et al., 2007). This amplitude reduction was usually found by recording the MMN to simple frequency or duration changes in sinusoidal tones, for instance, in schizophrenia (Todd et al., 2003; Javitt et al., 2000; Michie et al., 2000; see also Javitt et al., 1998). In schizophrenia, the duration MMN, in particular that to duration increment, was even more affected than that to frequency change (Michie, 2001; Michie et al., 2000; for a meta-analysis, see Umbrecht and Krijts, 2005). The frequency MMN is attenuated in amplitude in several other clinical groups, too, such as children with developmental dysphasia (Holopainen et al., 1997, 1998; Korpilahti and Lang, 1994), dyslexia (Baldeweg et al., 1999; Renvall and Hari, 2003; Kujala et al., 2003, 2006; Sebastian and Yasin, 2008) and SLI (Mengler et al., 2005; Rinker et al., 2007).

In children and adults with dyslexia, the MMN to frequency change but not that to duration change was considerably attenuated in amplitude (Baldeweg et al., 1999; Kujala et al., 2006). Furthermore, in keeping with this profile of MMN-amplitude reduction, the behavioural frequency but not duration discrimination was affected (Baldeweg et al., 1999). In addition, this frequency-MMN deficit strongly correlated with the severity of the reading problem. Subsequently, Lachmann et al. (2005)
showed that the MMN-attenuation profile involving frequency and consonant–vowel (CV) syllable changes could disentangle different diagnostic subgroups of developmental dyslexia from each other. Moreover, Shafer et al. (2005) and Uwer et al. (2002) found that SLI children had attenuated MMN amplitudes for syllable change.

Using the new multi-feature MMN 'optimum' paradigm (Näätänen et al., 2004), permitting one to obtain five different MMNs in 15 min, Lovio et al. (2010) found a widespread auditory discrimination deficit in children at risk for dyslexia. Their MMNs for consonant, vowel, vowel duration and intensity changes of syllables were diminished in amplitude. By contrast, Kujala et al. (2006), also using the multi-feature paradigm, found that in adult dyslexics, the frequency MMN was attenuated, whereas their location MMN was in fact enhanced in amplitude. This shows that not all changes in central auditory processing in dyslexia signify deteriorated discrimination. However, the MMN data may also suggest the presence of cognitive deficiencies associated with dyslexia, at least deficient phonotactic processing (Bonte et al., 2007).

Furthermore, in children with autism, the MMN to duration change (Lepistö et al., 2005) and the MMNm to speech-sound change (Kasai et al., 2005; for recent corroborating results, see Roberts et al., 2011) were attenuated in amplitude. In addition, the MMN to CV-syllable change was prolonged in peak latency but only in those children who preferred non-speech analogy signals to speech (Kuhl et al., 2005). By contrast, the MMN to frequency change was enhanced in amplitude (Lepistö et al., 2005; Ferri et al., 2003) and shortened in peak latency (Gomot et al., 2002) in autistic children, consistent with their better-than-average pitch discrimination and musical abilities (Bonneel et al., 2003; Heaton et al., 2001). Very recently, it was found by Roberts et al. (2011; see also Näätänen and Kujala, 2011) that in autistic children of 7–9 years, the MMNm peak latency for tone-frequency and vowel changes was delayed, in comparison with that of normally developing children of the same age, and, further, that this delay was considerably increased if the child also suffered from a delay in linguistic development. This might contribute to their speech-understanding difficulties and hence to their social isolation. In addition, in the Asperger syndrome, a condition belonging to the autism spectrum, the duration-increment MMN of children of about 9 years of age was attenuated in amplitude over the left hemisphere, whereas it was enhanced over the right hemisphere (Lepistö et al., 2006). Moreover, in this syndrome, the MMN amplitude was also attenuated for changes in prosody (Kujala et al., 2005a). Recently, a shortened MMN peak latency for frequency change and increased MMN amplitudes for duration and gap changes were found in Asperger adults by Kujala et al. (2007).

In addition, the MMNs for frequency and duration changes were attenuated in amplitude in patients with a left-hemispheric stroke (Csépe et al., 2001; Aaltonen et al., 1993; Auther et al., 2000; Ilvonen et al., 2001). These two MMNs showed somewhat different time courses of post-stroke recovery, however (Ilvonen et al., 2003) (Fig. 3). Importantly, the MMN recovery indexed that of speech perception, there being a correlation between the duration-MMN amplitude and the Boston Diagnostic Aphasia Examination Speech-Comprehension Test from 10 days to 3 months post-stroke onset (Ilvonen et al., 2003). Subsequently, Särkämö et al. (2010b) found that the MMNm recovery and behavioural discrimination could be expedited with music and speech stimulation. In addition, the MMNm recovery corre...
lated with the recovery of behavioural speech-sound discrimination.

In epilepsy, the MMN is also affected. The MMN peak latencies were abnormally long or no clear MMN response could be found for speech (but could for tones) in patients with benign childhood epilepsy with contra-temporal spikes (Boatman et al., 2008; Duman et al., 2008). Patients with such spikes with atypical features and learning difficulties also exhibit attenuated MMN amplitudes (Metz-Lutz and Philippini, 2006). In addition, in the Landau–Kleffner syndrome, an MMN was obtained for phoneme change but not for prosodic change (Honbolygó et al., 2006). By contrast, Miyajima et al. (2011) found that at fronto-central sites, their MMN amplitude for tone-duration discrimination was enhanced, interpreted by the authors as reflecting frontal-lobe hyperexcitability to compensate for temporal-lobe dysfunction indexed, according to the authors, by prolonged MMN peak latencies in patients relative to controls at both fronto-central and mastoid sites, consistent with previous reports (Lin et al., 2007; Borghetti et al., 2007). Furthermore, in the Miyajima et al. (2011) temporal-lobe epilepsy patients, the fronto-centrally recorded MMN persisted longer than that in controls, consistent with the results of Gene-Cos et al. (2005) who suggested that a prolonged MMN duration might point to difficulty in ‘the closure mechanism of the MMN process’.

The MMN can also be used to evaluate the possible central-auditory-processing damage associated with a very premature birth. Studying very prematurely born children (mean gestational age 29 weeks) with a very low birth weight (mean 1115 g), Jansson-Verkasalo et al. (2003b, 2004) found that their MMN amplitude for consonant change at 4 years (from conception) was smaller than that of controls and, further, that the absence of the MMN at 4–5 years of age predicted naming difficulties at 6 years. However, if the MMN amplitude nevertheless was normal at 4 years, then there were no naming difficulties at 6 years.

Moreover, the MMN enables one to also determine central-auditory-processing damage caused by long-term exposure to loud occupational noise. In workers exposed to such a noise for 2–17 years, the MMN to syllable change was attenuated in amplitude (even though their peripheral hearing was not affected), in keeping with their increased speech-perception problems (Kujala et al., 2004). In addition, the Brattico et al. (2005) MMN data showed that long-term exposure to occupational noise altered the cortical organisation of speech-sound processing in these workers (in the absence of peripheral hearing loss) but did not alter that of non-speech processing. In addition, the discrimination of auditory stimuli was generally slowed down, as indexed by prolonged MMN-peak latencies.

Furthermore, by using the MMN, one can also monitor age-related changes in central auditory processing (Fabiani et al., 2006; Woods, 1992; Woods and Clayworth, 1986; Jääskeläinen et al., 1999a; Kiang et al., 2009; Cooper et al., 2006; Gaeta et al., 1998, 2001, 2002; Kisley et al., 2005; Pekkonen et al., 2005; Pekkonen et al., 1995a, 1996a). A particularly convincing characterisation of the MMN–age relationship was provided by Kiang et al. (2009) who carefully plotted the MMN and P3a amplitudes for tone-duration increment across adulthood for 147 normal subjects and 253 schizophrenic patients (Fig. 4). Along with an increasing age, the

3. The MMN as an index of shortened sensory-memory duration (Table 2)

The MMN elicitation depends on the presence of the sensory-memory trace representing the preceding stimuli and their regularities at the moment of the delivery of a deviant stimulus (for a review, see Näätänen et al., 2007). Hence, by gradually prolonging the inter-stimulus interval (ISI), the MMN eventually vanishes, which enables one to assess sensory-memory duration in audition (a potential general index of brain plasticity; Näätänen and Kreepipuu, 2011).

In young healthy adults, the trace duration, as estimated in this manner, approximates 10 s (Böttcher-Gandor and Ullsperger, 1992; Sams et al., 1993), but is gradually shortened with ageing. With short ISIs such as 0.5 s, the MMN amplitude for frequency change was very similar in elderly (mean 59 years) and young (mean 25 years) male subjects, suggesting that the memory-trace formation for sounds and, thus, perception (see Näätänen and Winkler, 1999) were not affected by ageing. By contrast, with a stimulus-onset asynchrony (SOA) of 4.5 s, the MMN amplitude of the elderly was much more attenuated than that of the young (Pekkonen et al., 1996a) (Fig. 5), indicating that in ageing, the auditory sensory-memory duration is shortened. Moreover, corresponding MMN data for frequency change in chronic alcoholics suggest accelerated age-related shortening of the memory-trace duration in these patients (Polo et al., 1999; see also Grau et al., 2001).

The memory-trace duration is particularly short in patients with Alzheimer’s disease, of course. Their MMN was, however, normal with short ISIs (0.5 s), suggesting normal memory-trace formation/perception (see Näätänen and Winkler, 1999) even in these patients, but absent at long ISIs (3 s) (Pekkonen et al., 1994), indexing their extremely short sensory-memory duration. Interestingly, this data pattern is orthogonal to that observed in patients with schizophrenia in whom no normal-amplitude MMN can be obtained in any condition, not even with very short ISIs and wide frequency deviations (Javitt et al., 1998). This suggests that their memory-trace formation, and hence auditory perception

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<td>The MMN shows increased involuntary attention switching in:</td>
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<td>– Closed head injury (Kapio et al., 2000)</td>
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<td>– Ageing (Gaeta et al., 2001)</td>
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<td>– Alcoholism (Ahveninen et al., 2000b; Polo et al., 2003)</td>
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<tr>
<td>– Children with major depression (Lepistö et al., 2004)</td>
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<td>– Sleep disorder (Cunneyk et al., 2010)</td>
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<td>Fig. 5. MMN to frequency change (700 – 600 Hz) was normal in older males with an inter-stimulus interval (ISI) of 0.5 s but was considerably attenuated, relative to that of younger males, with an ISI of 4.5 s, indexing faster auditory sensory-memory trace decay with aging (From Pekkonen et al., 2001a).</td>
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level of performance in different cognitive tasks is gradually decreased (Cansino, 2009). There is also evidence linking these MMN changes to cognitive deterioration (Kisley et al., 2005). Even in healthy elderly persons, the MMN to a short gap in the middle of a tone (Desjardins et al., 1999) was attenuated in amplitude, indexing their increased difficulties in correctly perceiving rapid speech-sound patterns such as consonants (Bertioli et al., 2002, 2005).

The MMN and MMNm are also affected by different drugs (Table 1).
Table 6
The MMN correlates with structural changes in:

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<th>Condition</th>
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<td>Schizophrenia</td>
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<td>(Hirayasu et al., 2000, 2001; Kasai et al., 2003a,b; Park et al., 2002; Rasser et al., 2011; Salisbury et al., 2002, 2007; Yamase et al., 2004; Youn et al., 2003; for a review, see van der Stelt and Belger, 2007)</td>
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<td>Cleft palate (children with)</td>
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<td>(Ceponiene et al., 1999)</td>
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(Näätänen and Winkler, 1999), is abnormal, consistent with clinical observations (for a review, see Näätänen and Kähkönen, 2009). By contrast, their sensory-memory duration, as judged from the ISI–MMN relationship in these patients, is unaffected (Javitt et al., 1998; see also March et al., 1999).

The auditory memory-trace duration shows developmental changes also in the beginning of the life, but to the opposite direction, of course, being only 0.5 s in newborns, as judged from MMNs recorded during sleep (Cheour et al., 2002b), but is thereafter gradually prolonged during infancy and childhood. By using the Grau et al. (1998) paradigm for effectively determining the sensory-memory duration, Glass et al., 2008a,b found that this duration was about 1–2 s at the age of 2–3 years but was prolonged to 3–5 s by the age of 6 years (see also Gomes et al., 1999).

This memory-trace duration is affected in some child patient groups, too. In children of 7–8 years with cleft palate, the MMN for tone-frequency change was of normal amplitude with short SOAs (350 and 700 ms), whereas the prolongation of the SOA to 1400 ms attenuated this amplitude more than it attenuated that of control children (Ceponiene et al., 1999) (Fig. 6). Furthermore, an analogous data pattern was obtained in small infants with cleft palate, which was even more abnormal in children with the CATCH-22 syndrome (Cheour et al., 1997, 1999a, 1999).

In addition, a short auditory sensory-memory duration even in normal healthy children is associated with delayed linguistic development. Late talkers had a shorter sensory-memory duration than that of controls, as judged from MMN data for tone-frequency change as a function of the ISI suggested a shorter auditory sensory-memory duration in parents of children with SLI than that in parents of normally developing children.

4. The MMN as an index of abnormal auditory perception

In the foregoing, it was already mentioned that in patients with schizophrenia, no normal-size MMN can be obtained irrespective of experimental manipulations, not even with very short SOAs (Javitt et al., 1998). This suggests a fundamental abnormality in memory-trace formation, and thus in auditory perception (see Näätänen and Winkler, 1999), in these patients (Näätänen and Kähkönen, 2009). Moreover, a number of further studies in patients with schizophrenia (Oades et al., 1996; Hirayasu et al., 1998; Schall et al., 1999; Youn et al., 2003; Kasai et al., 2002a,b) showed that the frequency-MMN amplitude deficit tends to correlate with the severity of auditory hallucinations. In addition, Youn et al. (2003) found that the abnormality of the left–right MMN-amplitude asymmetry for frequency change of a tone correlated with the positive scores of the positive-and-negative syndrome scale (PANSS), in particular with its hallucination subscale. For corroborating MMN data, see Thonnnesen et al. (2008). Moreover, Fisher et al. (2008) found a smaller duration-MMN amplitude in patients with auditory hallucinations than in those with no hallucinations. In addition, the MMN amplitude for intensity change was also smaller in hallucinating than non-hallucinating patients. Furthermore, both patient groups showed an attenuated MMN amplitude for frequency change. This MMN deficiency however was differently distributed in frontal areas in the two patient groups.

5. The MMN as an index of increased backward masking (Table 3)

Auditory masking refers to any observation such that information in a test auditory stimulus is reduced by the presentation of another (masking) auditory stimulus (Massaro, 1973). The perception of sequentially presented auditory stimulation may be hindered by backward masking, with a sound preventing the perception of an immediately preceding sound, apparently by affecting its memory-trace formation (Massaro, 1975), in particular when the later sound is stronger in intensity than the preceding sound (see Hawkins and Presson, 1986). Massaro (1975) concludes that backward masking occurs because the masking stimulus essentially overwrites the auditory image of the test stimulus and, therefore, terminates the perceptual processing of the test stimulus.

Backward masking can be assessed both behaviourally and by using the MMN: a masker presented shortly after each stimulus of the oddball paradigm causes the MMN to deviants and the subject’s ability to discriminate them behaviourally to disappear in parallel (Winkler and Näätänen, 1994; Winkler et al., 1993). By using this type of paradigm, it was found by Kujala et al. (2003) that backward masking is enhanced in dyslexic individuals. Increased backward masking, as reflected by MMN-data pattern, was also reported in chronic alcoholism (Ahveninen et al., 1999).

Importantly, this MMN deficit in chronic alcoholism correlated with the amount of their alcohol consumption and predicted their working-memory performance deficit (Ahveninen et al., 1999).

6. The MMN as an index of abnormal involuntary attention switching: either too weak (Table 4) or too strong (Table 5)

As already mentioned, in addition to its auditory-cortex generators, the MMN also has a frontal (usually right-hemispherically predominant (Giard et al., 1990)) generator contributing, together with the auditory-cortex MMN generator (see Fig. 2), to the frontally and centrally recorded MMN amplitudes (Deouell, 2007; Giard et al., 1990; Rinne et al., 2000). The frontally recorded MMN amplitude is considerably attenuated, whereas the
Table 7
The MMN indexes pathological brain excitability in:
- Alcoholism (Ahveninen et al., 2000a; Pekkonen et al., 1998)
- ALS (with bulbar signs) (Pekkonen et al., 2004)
- Chronic primary insomniaa (Wang et al., 2001)
- Epilepsy (Myajima et al., 2011)
- Huntington’s disease, Sydromatic Phase (Beste et al., 2008)
- Major depression, children with (Lepistö et al., 2004)
- Pediatric migraine (Valeriani et al., 2008; see, however, de Tommaso et al., 2004)
- Schizophrenia (pathological microglia activation, indexing local disease process and neuronal death) (Banati and Hickie, 2009)
- Stuttering (Corbera et al., 2005; see also Wu et al., 1997)

Table 8
The MMN indexes cognitive and functional decline in:
- Ageing (Gaeta et al., 2002; Kisley et al., 2005; Schroeder et al., 1995)
- Alzheimer’s disease and dementia (Engeland et al., 2002; Schroeder et al., 1995)
- Amyotrophic lateral sclerosis (ALS) (Raggi et al., 2008)
- Autism (Seri et al., 2007; Roberts et al., 2008, 2011; Näätänen and Kujala, 2011)
- CATCH-22 syndrome: children (for a review, see Cepioniene et al., 2002), adults (Baker et al., 2005)
- Children with cleft palate (Cepioniene et al., 2002)
- Chronic alcoholism (Polo et al., 1999)
- Coma, survivors of (Kane et al., 2000)
- Developmental dysphasial (Holopainen et al., 1997, 1998; Korpihieti and Lang, 1994)
- Diabetes mellitus (advanced phase) (Vanhanen et al., 1996)
- Down’s syndrome (Lalo et al., 2005)
- Dyslexia (Bonte et al., 2007)
- Epilepsy (Boatman et al., 2008; Liass et al., 2000, 2001, 2006; Metz-Lutz and Philippini, 2006)
- HIV (Schroeder et al., 1994)
- Intellectual disability (Ikeda et al., 2004; Nakagawa et al., 2002)
- Multiple sclerosis (MS) (Gill et al., 1993; Jung et al., 2006; Santos et al., 2006)
- Parkinson’s disease (Branick et al., 2010; Karayanidis et al., 1995; Pekkonen et al., 1995c)
- Persistent vegetative state (PVS), survivors of (Kotchoubey, 2007; Wijnen et al., 2007; van der Stelt and van Boxtel, 2008; Zarza-Lucianez et al., 2007)
- Preterm children with very low birth weight (Jonsen-Verkasalo et al., 2004, 2010)
- REM-sleep deprivation (Zourouli et al., 2010)
- Schizophrenia (e.g., Baldeweg et al., 2004; Hermens et al., 2010; Kawakubo et al., 2007; Light and Braff, 2005a,b; Rasser et al., 2011; Toyomaki et al., 2008)
- Sleep deprivation (Raz et al., 2001)
- Stroke and aphasia (Author et al., 2000; Iivonen et al., 2003, 2004; Pettigrew et al., 2005; Särkämö et al., 2009, 2010a,b; Wertz et al., 1998)
- Velo-cardio-facial syndrome (Baker et al., 2005)

A similar (but transient) dampening of involuntary attention switching can also be observed in acute alcohol intoxication (Jääskeläinen et al., 1995, 1996a,b, 1998, 1999b). Even a moderate dose of ethanol selectively weakened the frontal-MMN process, whereas the supratemporal MMN process (with most of it being separately observable in nose-referenced mastoid recordings) was unaffected (Jääskeläinen et al., 1996b) (Fig. 2). Furthermore, ethanol abolished the performance decrement caused by auditory distraction in a visual task (Jääskeläinen et al., 1999b), i.e., dampened the effects of auditory distracting stimuli on brain mechanisms controlling for environment-driven involuntary attention switches in audition (Escera et al., 2000a; Escera and Corral, 2007; Jääskeläinen et al., 1999b). This explains, in part, why alcohol increases accident risk in traffic (cf. Näätänen and Summala, 1976). In addition, the Alho et al. (1994) MMN data suggested decreased involuntary attention switching to auditory changes as a consequence of a frontal-lobe lesion (see Table 4).

Conversely, the frontal involuntary attention-switching mechanism may also become too sensitive, in this way disturbing primary-task performance (Table 5). In patients with closed head injury suffering from dramatically increased distractibility, this mechanism is abnormally sensitive, judging from their very large frontally recorded MMN amplitudes at the presence of normal mastoid-recorded (nose-referenced) MMN amplitudes (Kaijio et al., 1999, 2000) (cf. Fig. 2). A subsequent study (Polo et al., 2002) did not confirm this finding, however, which might result from the abnormally fast vigilance decrement of these patients (Kaijio et al., 2001).

Moreover, in children suffering from major depression, shortened MMN latencies and increased P3a amplitudes (an index of the occurrence of an attention switch; Squires et al., 1975; Escera et al., 2000a) might be associated with these patients’ increased distractibility and difficulties in concentrating on task performance, as shown by the Lepistö et al. (2004) MMN data for CV-syl-lable change. Analogous MMN evidence for increased distractibility was also obtained in chronic alcoholism (Ahveninen et al., 2000a,b) and ageing (Gaeta et al., 2001).

7. The MMN attenuation caused by cerebral grey-matter loss or other structural change (Table 6)

The MMN is also attenuated by structural damage in the central auditory system and even elsewhere in the brain. In schizophrenia patients, a gradual loss of the left-hemisphere temporal grey-matter volume has been observed, which was reflected by attenuated MMN amplitudes for frequency change (Hirayasu et al., 1998). More recently, Salisbury et al. (2007) found, by using magnetic resonance imaging (MRI), that at first hospitalisation, schizophrenia patients’ left Heschl-gyrus volume did not differ from that of bipolar-disorder patients and normal controls and, further, that this was reflected by similar MMN amplitudes for tone-frequency change. However, in an 18-month follow-up, this volume was reduced in schizophrenia patients only, and the magnitude of the Heschl’s gyrus volume reduction in these patients strongly correlated with the parallel attenuation of their MMN amplitude. Also, Yamase et al. (2004) found that in schizophrenia patients, MMNn deficiency for phoneme change in the left hemisphere correlated with the magnitude of the left planum-temporale grey-matter loss, suggesting that these structural abnormalities may underlie the functional abnormalities of fundamental language-related processing in these patients. In addition, very recently, Rasser et al. (2011) found that MMN-amplitude attenuation for frequency change in patients with schizophrenia (reflecting their impaired day-to-day functioning level) correlated with the magnitude of grey-matter loss in the left Heschl’s gyrus as well as in the motor and executive
Fig. 7. Post Hoc correlation analyses of reduced gray matter measures – averaged over specific gyri defined on the Deformed "Montreal Neurological Institute" brain template – with reduced frequency mismatch negativity (MMN) peak amplitudes recorded at fronto-central electrodes in control subjects (blue) and schizophrenia patients (Red). Solid regression lines indicate significant correlation ($P < .05$, uncorrected) (From Rasser et al., 2011).
regions of the frontal cortex while MMN reduction for duration deviants also correlated with grey-matter loss in the right Heschl’s gyrus (Fig. 7).

It is possible that the MMN deficiency observed in schizophrenia can be linked to grey-matter loss occurring in these patients. Olney and Farber (1995) suggested that N-methyl-D-aspartate (NMDA)-receptor (NMDAR) hypofunction accounts for structural brain changes in these patients. The data reviewed by the authors showed, among other things, that a repeated treatment with an NMDA antagonist during a 3- to 4-day period induces a pattern of neurodegenerative changes distributed over several corticolimbic brain regions. The authors concluded that these and other findings signify that the persistent suppression of the NMDAR function lasting for a few days only can lead to relatively subtle but permanent structural changes that are distributed over the neocortical and limbic brain regions in a pattern roughly similar to the pattern of structural changes observed in schizophrenia (Bogerts, 1993). The fact that the MMN is an index of NMDAR dysfunction would then explain the relationship between MMN deficiency and grey-matter loss (Salisbury et al., 2007; Rasser et al., 2011).

The MMN can also reflect structural changes (craniofacial malformations) associated with cleft palate (for a review, see Ceponiene et al., 2002). In children with cleft palate of 7–9 years of age, it was found by Ceponiene et al. (1999) that the more posteriorly delimited the cleft was, the smaller was the MMN amplitude for tone-frequency change and the more severe was the cognitive defect.

8. The MMN as an index of pathological brain excitation/excitability (Table 7)

In some conditions, an increased MMN amplitude appears to index pathologically increased central nervous system (CNS) or central-auditory-system excitation/excitability. For example, in abstinent chronic alcoholics, the MMN for frequency change was abnormally enhanced in amplitude, which might be associated with their increased distractibility (Ahveninen et al., 2000a,b). In addition, in patients with persistent developmental stuttering, the MMN to phonetic contrasts was strongly enhanced in amplitude, whereas that to simple tone contrasts (both frequency and duration) was unaffected (Corbera et al., 2005). This might index abnormal excitability located specifically in the speech-sound MMN generation region (Näätänen et al., 1997). This MMN finding correlated with the patients’ subjective appraisal of their speech-production problems. These results might indicate that proper speech production requires the presence of stable sensory reference provided by the speech-sound-specific memory traces of the left temporal cortex (Näätänen, 2001; Näätänen et al., 1997; Shestakova et al., 2003).

In the same vein, an MMNm enhancement to tone-duration decrement found by Pekkonen et al. (2004) in patients with ALS with bulbar signs might result from cortical overactivity of excitatory neurotransmitter glutamate observed in ALS (Rowland and Shneider, 2001). Raggi et al. (2008), however, found MMN-amplitude decrement for frequency change in non-demented patients with sporadic ALS.

Consistent with the Pekkonen et al. (2004) above-reviewed ALS results, at late, symptomatic, stages of Huntington’s disease, the MMN to frequency change was considerably enhanced in amplitude, along with behavioural improvement in an auditory signal-detection task, compared to the control group and Huntington patients in the early, presymptomatic, stage (Beste et al., 2008). This paradoxical effect, as contrasted to effects of neurodegenerative diseases in general, was attributed by the authors to toxic-level overexcitability of the NMDAR system (due to increased glutamate concentrations).

In addition, very importantly, Banati and Hickie (2009); (see also Banati, 2003) found in patients in schizophrenic psychosis that MMN deficiency for frequency and duration deviants indexed pathological microglia (the main constituent of the brain’s innate immune system) activation, reflecting local ‘disease activity’ and neuronal death in these patients. The authors emphasised that this microglia activation is not a diagnostically specific pathological process but rather that this activation can serve as a generic marker that relates more directly to disease progression and may be correlated with other meaningful illness measures such as the MMN.

Pathological brain excitation, as suggested by increased MMN amplitudes, can also be found in temporal-lobe epilepsy (Miyajima et al., 2011; Gene-Cos et al., 2005) even though MMN peak latencies may be prolonged, a possible sign of central-auditory-processing disturbance in these patients (Miyajima et al., 2011).

Pathological excitation might also explain some results in patients suffering from post-traumatic stress disorder (PTSD), who showed considerably elevated MMN amplitudes for frequency change (Morgan and Grillon, 1999; Ge et al., 2011), whereas Menning et al. (2008) could not confirm these results.

9. The MMN as an index of cognitive and functional deterioration (Table 8)

Baldeweg et al. (2004) found a relationship between the frontally recorded duration-increment MMN deficit and impairments in memory functions of patients with schizophrenia, which are evident in these patients (Sullivan et al., 1995; Jahshan et al., 2010). Subsequently, Light and Braff (2005a) obtained a strong correlation between the global-assessment-of-functioning (GAF) ratings and the fronto-central MMN amplitude for tone-duration prolongation in these patients. Furthermore, the MMN amplitude was highly predictive of the patients’ level of independence in their domestic life. This correlation was replicated in longitudinal studies 1–2 years later, indicating a stable relationship (Light and Braff, 2005b). Subsequently, the relationship between the duration-increment MMN amplitude and patients’ functional status was also found by Kawakubo et al., 2007; social skills acquisition) and by Toyomaki et al. (2008; executive functioning). (For corroborating results with the frequency-MMN amplitude, see Rasser et al. (2011).) Interestingly, this relationship for duration-increment MMN amplitude is also present in normal healthy subjects (Light et al., 2007). For previous analogous results with the frequency-MMN amplitude in normal healthy subjects, see Bazana and Stelmack (2002) and Beauchamp and Stelmack (2006), and with the MMN amplitude for syllable change in children, Liu et al. (2007). For recent corroborating results, see Troche et al. (2009, 2010).

In a similar vein, Jung et al. (2006) found that the MMN-amplitude attenuation for duration decrement in patients with MS indexed cognitive decline occurring in part of these patients, being larger in magnitude for greater cognitive loss. For corroborating results, see Gil et al., 1993) and Santos et al. (2006). Furthermore, MMN (MMNm) deficit indexes cognitive decline also in chronic alcoholism (Polo et al., 1999, 2003), stroke (Iivonen et al., 2003;
Särkämö et al., 2009, 2010a.; Author et al., 1998, 2000; Pettigrew et al., 2005; Wertz et al., 1998), epilepsy (Boatman et al., 2008; Liasis et al., 2006), velo-cardio-facial (DiGeorge) syndrome (Baker et al., 2005), Down’s syndrome (Lalo et al., 2005), children with certain forms of cleft palate and those with the Catch-22 syndrome (Ceponiene et al., 2002) and, of course, in Alzheimer’s disease (Pekkonen et al., 1994; vMMN: Tales and Butler, 2006; Tales et al., 2008), dementia (Schroeder et al., 1995), intellectual disability (Nakagawa et al., 2002; Ikeda et al., 2004) and mild cognitive impairment (MCI) (vMMN: Tales and Butler, 2006; Tales et al., 2008).

MMN-amplitude attenuation (at least for frequency change) can also index cognitive and functional degeneration in patients with an advanced stage of diabetes mellitus (Vanharen et al., 1996), Parkinson’s disease (Karayanidis et al., 1995; Pekkonen et al., 1995b; Brønnick et al., 2010), HIV (Schroeder et al., 1994) and also in normal ageing (Gaeta et al., 2001; Kisley et al., 2005; Cooper et al., 2006). In addition, the MMN amplitude indexes decreased cognition in different subnormal states such as sleep deprivation (Raz et al., 2001), rapid eye movement (REM)-sleep deprivation (Zerouali et al., 2010) and in patients in the comatose (Fischer et al., 1999, 2006b) or PVS (Wijnen et al., 2007) state.

Recently, Bisachi et al. (2009) found smaller-amplitude MMN responses to tone-frequency change in newborns of less than 30 gestational weeks than in those with a longer gestational period. This amplitude strongly correlated with several maturational factors (gestational age, weight, length and cranial circumference). These results suggest, according to the authors, the role of the gestational age as the main factor explaining cortical functioning at the early age.

10. The MMN as an index of the level of consciousness (Table 9)

In patients in the 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 as a tool in coma-outcome prediction (Kane et al., 1993, 1996; Fischer et al., 1999, 2004, 2006a,b; Luauté et al., 2005; Morlet et al., 2000; Fischer and Luauté, 2005; Daltrozzo et al., 2007; Vanhaudenhuyse et al., 2008). Moreover, the MMN peak latency measured at hospitalisation 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 (2007) stressed that in using the MMN for the objective assessment of the patient’s remaining cognitive capacity, it is better to use complex rather than simple sound stimuli which may result in severe underestimation of the remaining capacity. For a meta-analysis of studies on the MMN in coma, see Daltrozzo et al. (2007). Recently, it was concluded by Vanhaudenhuyse et al. (2008) that MMN results in comatose patients converge to the conclusion that MMN is a very good predictor of recovery from coma, in particular in anoxic coma.

In patients in the PVS, the frequency-MMN recovery occurred in parallel with the recovery of consciousness (Wijnen et al., 2007; Kotchoubey, 2007; Kotchoubey, 2007), showing a step-wise ampli-

tude increase when the patient crossed the boundary from unconsciousness to consciousness. In addition, in locked-in patients, the frequency MMN can give evidence for the presence of at least some level of consciousness (Ragazzoni et al., 2000). Moreover, the MMN can also index anaesthesia depth (for a review, see Heinke and Koelsch, 2005): a small-amplitude MMN was recorded to frequency change during deep sedation, whereas in complete unconsciousness, this MMN was absent. It, however, returned while the patient was recovering from anaesthesia (Heinke et al., 2004). Interestingly, an MMN type of response was also elicited by music-syntactic violations in deep sedation (Heinke et al., 2004; Koelsch et al., 2006), indicating that this kind of complex analysis following the rules of Western music can occur even in deep sedation.

Very recently, it was found by Boly et al. (2011) that in the vegetative state, feed-forward processes are preserved whereas top-down processes are impaired. The effective connectivity was measured by using the MMN for tones presented in a roving paradigm (Baldegeweg et al., 2004). The authors found that the only difference between patients in the vegetative state and controls was an impairment of backward connectivity from frontal to temporal cortices, suggesting that a selective disruption of top-down processes from high levels of a cortical hierarchy can lead to loss of consciousness in brain-damaged patients, and can clearly differentiate the vegetative state from minimally conscious state. In addition to its neuroscientific relevance, the present approach could, according to Boly et al. (2011), constitute a new diagnostic tool to quantify the level of consciousness electrophysiologically at the patients’ bedside.

The MMN can also reflect effects of hypnosis (Jamieson et al., 2005; Kallo et al., 1999) and concentrative meditation (Srinivasan and Baijal, 2007).

11. The MMN as an index of the progression/severity of the illness (Table 10)

In patients with schizophrenia, the MMN amplitude in particular to frequency change is attenuated concomitantly with disease progression (for a meta-analysis, see Umbricht and Krljes, 2005). Consistent with this, several studies (Salisbury et al., 2002, 2007; Umbricht et al., 2006; Devrim-Ucok et al., 2008; Todd et al., 2008) showed that the frequency MMN deficit was more robust in chronic patients than in first-episode patients in whom the effect was smaller in size or had not yet emerged. In addition, Shinozaki et al. (2002) found that a temporary recovery of acute symptoms of schizophrenia patients was accompanied by an MMN amplitude increase for tone-frequency change recorded at mastoids as polarity-reversed MMN (whereas the frontally recorded MMN did not correlate with this temporary recovery). In addition, Urban et al. (2008), using the vMMN, found that the reduction of its amplitude for motion-direction deviants was larger for a more severe state and longer duration of the illness of the patient.

Moreover, MMN data also reflected clinical severity in patients with persistent developmental stuttering (Corbera et al., 2005), dyslexia (Baldegeweg et al., 1999; Stoodley et al., 2006), PTSD (Menning et al., 2008) and in newborns and 6-month-old infants with cleft palate (with clinical severity being determined as the anterior-posterior extent of the cleft; Ceponiene et al., 1999, 2000a,b, 2002). In a similar vein, Moberget et al. (2008) found that patients exhibiting the most severe symptoms of ataxia, a sign of cerebellar cortical atrophy, produced smaller-amplitude MMN responses to tone-duration change than other patients.

Studying stroke patients, Särkämö et al. (2008, 2009, 2010a, b) addressed amnesia caused by a left or right middle cerebral artery
stroke. They found that amusia caused by a right-hemisphere dam-
age, especially that to temporal and frontal areas, was more severe than that caused by a left-hemisphere damage. Furthermore, in amusia right-hemisphere patients, the severity of amusia corre-
lated with weaker frequency-MMN responses. Additionally, within the right-hemisphere-damaged group, the amusic patients who had damage in the auditory cortex showed worse recovery from amusia as well as weaker MMNm responses throughout the 6-month follow-up than did the non-amusic patients or the amusic patients with no auditory-cortex damage. Also, the amusic patients (both with and without auditory-cortex damage) performed worse than did the non-amusic patients on a number of tests of different aspects of cognitive performance (including working memory, attention, and cognitive flexibility). These findings suggest, 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 associ-
ated with both auditory and cognitive deficits.

In conclusion, because of the large number of different disor-
ders affecting the MMN, it appears that the MMN provides a gen-
eric illness measure, useful for assessing illness severity, as suggested by Banati and Hickie (2009) for both the MMN and microglia activation.

12. The MMN in predicting illness course/drug response (prognosis) (Table 11)

A striking finding was that the recovery of the MMN in a coma-
tose patient strongly predicted, as already mentioned, the recovery of consciousness in the near future (Kane et al., 1993, 1996; Fischer et al., 2000, 2006a,b; Morlet et al., 2000; Naccache et al., 2005; Vanhaudenhuyse et al., 2008 (with the MMN being the best predictor of positive outcome, i.e., recovery without getting into the persistent vegetative state; Fischer and Luauté, 2005; Luauté et al., 2005); for a meta analysis, see Daltrozzo et al., 2007)

- Recovery from coma (Daltrozzo et al., 2007; Fischer and Luauté, 2005; Fischer et al., 1999, 2002, 2004, 2006a,b; Morlet et al., 2000; Naccache et al., 2005; Vanhaudenhuyse et al., 2008 (with the MMN being the best predictor of positive outcome, i.e., recovery without getting into the persistent vegetative state; Fischer and Luauté, 2005; Luauté et al., 2005); for a meta analysis, see Daltrozzo et al., 2007)

- Recovery from the persistent vegetative state (Kotchoubey, 2007; Kotchoubey et al., 2007; Wijnen et al., 2007 (with the MMN recorded at hospitalization also predicting the level of consciousness at discharge and even the extent of cognitive recovery during the next 2 years; Wijnen et al., 2007))

- Recovery from locked-in state (Ragazzoni et al., 2000)

- Recovery from alcoholism (Kothmann et al., 1995; Pekkonen et al., 1998)

- Social-skills learning in schizophrenia (Kawakubo et al., 2007)

- Social cognition in schizophrenia (Wyrm et al., 2010)

- Schizophrenia (first-episode onset) risk (Bodatch et al., 2011; Stone et al., 2010)

- Progression of schizophrenia (Bodatch et al., 2011; Devrim-Ucok et al., 2008; Kawakubo et al., 2007; Kiang et al., 2009; Light and Braff, 2005b; Salisbury et al., 2007; Umbricht and Krijes, 2005; Umbricht et al., 2006)

- Dyslexia (Blitz et al., 2007; Leppänen et al., 2010; van Leeuwen et al., 2006; Stoddley et al., 2006)

- Language development (Choudhury and Benasich, 2011; for a review, see Stix, 2011)


- Drug-therapy outcome in schizophrenia (Horton et al., 2010; Javitt et al., 2008; Lavoie et al., 2007; Schall et al., 1999)

- Working-memory performance decrement in chronic alcoholism (Ahveninen et al., 1999)

Furthermore, in patients with schizophrenia, MMN data can predict future developments of the patient’s state and the ef
ciciency of different treatments. For example, Umbricht et al. (2006) found that MMN deficiency at illness onset may index the presence of a more pervasive brain pathology and be observed only in a subgroup of patients, possibly in those with more precursors of schizophrenia or with an elevated risk of developing chronic schizophrenia. In addition, Kawakubo et al. (2007) found that the MMN in patients with schizophrenia was predictive of the acquisi-
tion of social skills during a 3-month social skills training programme.

Table 12

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<th>Table 12 The MMN showed increased genetic risk of:</th>
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<tr>
<td>- Alcoholism (Rodriguez et al., 1998; Zhang et al., 2001)</td>
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<td>- Asperger syndrome (Jansson-Verkasalo et al., 2005; Karpal atbi et al., 2007)</td>
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<td>- Dyslexia (Blitz et al., 2007; Friedrich et al., 2004; Leppänen et al., 2002, 2010; Leppänen and Lytinen, 1997; Lytinen et al., 2001, 2004, 2006; Maurer et al., 2009; Pihko et al., 1999; Richardson et al., 2003; van Leeuwen et al., 2006)</td>
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<td>- Language learning impairment (LLI) (Benasich et al., 2006; Choudhury and Benasich, 2011; Friedrich et al., 2004; Weber et al., 2005)</td>
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<td>- Schizophrenia in children (Schreiber et al., 1992), adults (Ahveninen et al., 2008; Bodatch et al., 2011; Brockhaus-Dumke et al., 2005; Hall et al., 2007, 2009; Jessen et al., 2001; Magno et al., 2008; Michie et al., 2002; Shin et al., 2009), and in Individuals with the CATCH syndrome (with a higher risk in individuals carrying the COMT(108/158) Val than COMT(108)/Met allele) (Baker et al., 2005)</td>
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<td>- Specific language impairment (SLI) (Barry et al., 2008; Benasich and Tallal, 2002; Benasich et al., 2006; Friedrich et al., 2004; Weber et al., 2005)</td>
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Fig. 8. Grand-average difference waves showing the duration mismatch negativity in the frontal (upper row) and central electrodes (lower row) for converting (dashed line) and nonconverting subjects (solid line). AR-C = at risk – coinversion, AR-NC = at risk – no conversion (From Bodatch et al., 2011).
Table 13
MMN indexes central-auditory-processing improvement in:

- Autistic patients (with frequency processing better than in Controls; Gomot et al., 2002)
- Children with specific language impairment (SLI) receiving language and speech training (Pihko et al., 2007)
- Cochlear-implant (CI) patients as a function of time since CI installation (Kraus et al., 1993b; Lonka et al., 2004; Ponton et al., 2000; Ponton and Eggermont, 2001) and training (Ponton et al., 2008)
- Dyslexic children presented with consonant–vowel syllables with lengthened formant-transition duration (Bradlow et al., 1999)
- Dyslexic children receiving audio-visual rehabilitation (Kujala et al., 2001)
- Early Child development, mainly speech-sound learning (Alho and Cheour-Luhtanen, 1997; Alho et al., 1990; Carral et al., 2005; Cheour et al., 1998b, 2002a,b; Cheour-Luhtanen et al., 1996; Choudhury and Benasich, 2011; Draganoa et al., 2005, 2007; Gomes et al., 2000; Gomot et al., 2000; Fellman and Huotilainen, 2006; Huotilainen et al., 2005, 2007; Kraus and Cheour, 2000; Kraus et al., 1992, 1993a, 1999; Kuhl, 2004; Kujala et al., 2004; Kushnerenko et al., 2002, 2007; Leppänen et al., 2004; Lovio et al., 2009; Lyrrinen et al., 2001, 2006; Molholm et al., 2004; Novitski et al., 2007; Oades et al., 1996; Pang et al., 1998; Pihko et al., 2005; Tanaka et al., 2001; Trainor et al., 2003; Uwer and von Suchodolletz, 2000)
- Early-onset blindness (Kujala et al., 1995a,b, 2000b, 2005b; Alho et al., 1993)
- Epileptic patients with vagus-nerve stimulation (Borgghetti et al., 2007)
- Infants operated for craniosynostosis (Huotilainen et al., 2008)
- Patients with hearing aids (Rudner et al., 2008)
- Patients with ultrasound hearing aids (Hosoi et al., 1998)
- Schizophrenic patients progressing from the Acute to Post-Acute Phase (Shinozaki et al., 2002)
- Sleeping infants exposed to auditory discrimination training (Cheour et al., 2002a)
- Stroke patients as a function of time since stroke onset (Ivonen et al., 2003; Sarkämö et al., 2010a)
- Stroke patients receiving music or audio-book stimulation (Sarkämö et al., 2010a)

see Coyle, 2006; Schwieler et al., 2008). Hence, an MMN enhancement may precede improvement in clinical severity, which, according to the authors, highlights the possible utility of the MMN as a biomarker of treatment efficacy, and, therefore, also as an end-point tool in drug development (see also Javitt, 2007, 2009; Javitt et al., 2008)

13. The MMN as an index of genetic disposition to different pathologies (Table 12)

Some studies suggest that in schizophrenia there is a genetic contribution to its aetiology. An MMN-amplitude attenuation for duration increment was found by Michie et al. (2002) and that for frequency change by Jessen et al. (2001) in symptom-free first-order relatives of patients with schizophrenia but studies with larger samples have either not confirmed these findings (Bramon et al., 2004) or showed a trend only (Price et al., 2006). However, Hall et al. (2006) recently found a significant, although modest, genetic correlation between the duration-increment MMN-amplitude deficit and schizophrenia, and therefore suggested that the MMN is a potentially valid endophenotype in schizophrenia. By contrast, Ahveninen et al. (2006), using the MMN to tone-frequency changes in their study of twin pairs discordant for schizophrenia, obtained results suggesting, according to the authors, that MN abnormalities in patients with schizophrenia might reflect predominantly state-dependent neurodegeneration. A similar conclusion was made by Magni et al. (2008) on the basis of their duration- and frequency-MMN amplitude results.

In patients with the 22q11 deletion syndrome, the considerably increased rates of schizophrenia are attributed to the loss of one allele containing the catechol-O-methyl transferase (COMT) gene. Symptom-free carriers showed attenuated MMN amplitudes for both simple auditory (duration and frequency) and syllabic changes as well as corresponding decrements in behavioural sound discrimination (Baker et al., 2005). Moreover, these MMN and behavioural effects were stronger in subjects carrying the COMT 108/158Met allele on their single intact chromosome (associated with a greater risk of schizophrenia) than in those carrying the COMT 108/158Val allele (a smaller schizophrenia risk). The authors
concluded that because the MMN depends on the NMDAR function (Javitt et al., 1996), the MMN modification by the COMT Val 108/158Met polymorphism points towards abnormal dopamine–glutamate interactions in the MMN-generator system.

Furthermore, children with a parent or sibling with dyslexia have an increased risk of dyslexia, and this is reflected by their attenuated MMN amplitudes to simple frequency (Maurer et al., 2003) or duration changes (Friedrich et al., 2004; Leppänen et al., 2002) or to phoneme-category change (van Leeuwen et al., 2006). Similarly predictive were the lack of a left-hemisphere MMN response to speech-sound change (Maurer et al., 2003) and the bilateral distribution of this MMN response (Maurer et al., 2009).

Also, studying 6-month-old infants with a family history of language-related learning difficulties, Benasich et al. (2006) found that these infants had smaller mismatch responses (MMRs; the positive-polarity analogue of MMN; Maurer et al., 2003) than those of control infants with no such family history. In addition, as already mentioned, Barry et al. (2008) obtained MMN data suggesting that parents of children with SLI have a shorter auditory sensory-memory duration than that of control parents.

Very recently, a major breakthrough in the research of the genetic background of dyslexia was made by Roeseke et al. (2011) who found that a certain marker (rs4234898), located on chromosome 4q32.1, was associated with the MMN deficit for a CV-syllable change. Moreover, this MMN was also associated with a two-marker haplotype of rs4234898 and rs1100040, one of its neighbouring single-nucleotide polymorphisms. The authors concluded that their results suggest a possible transregulation effect on SLC2A3, the predominant facilitative glucose transporter in neurons, which might lead to glucose deficits in dyslexic children and could explain their attenuated MMN in passive listening tasks, as observed in this study. Moreover, in a very recent study of the same group, Czamara et al. (2011) obtained results pointing to an association between the late MMN for speech-sound change and rare variants in a candidate region for dyslexia.

14. The MMN as an index of central auditory processing improvement or recovery (Table 13)

Spontaneous and training-induced improvement. A number of studies in normal healthy subjects (Atienza and Cantero, 2001; Kraus et al., 1995; Gottselig et al., 2004; Menning et al., 2000; Tremblay et al., 1997, 1998; Näätänen et al., 1993; for a review, see Kujala and Näätänen, 2010) demonstrated that the MMN reflects plastic neural changes associated with discrimination learning. Therefore, it is a very attractive tool for following up recovery and intervention effects in various patient groups, for instance, in stroke, coma, PVS or cochlear-implant (CI) patients or in children with developmental disorders.

In stroke and other brain-injured patients, it would be important to determine the changes in perceptual abilities very soon after the damage. However, such patients are often unable to cooperate or to understand instructions, particularly if the neural network involved in speech perception is affected. Aaltoinen et al. (1993), in an early study, found that the MMN to speech-sound change was abolished in posterior left-hemispheric stroke patients, whereas an anterior left-hemispheric stroke had no such effect. By contrast, the tone-frequency MMN was normal in both patient groups. Subsequently, as already mentioned, Ilvonen et al. (2003) followed up the recovery of left-hemisphere stroke patients, recording the MMN at 4 and 10 days, and then at 3 and 6 months after stroke onset. Language-comprehension tests (Boston Diagnostic Aphasia Examination and Token tests) were also administered in all but the first session in which the patients could not cooperate. The MMNs in the first two sessions were quite small in amplitude for sound-duration and -frequency changes, but became larger thereafter, disclosing normal-like amplitudes at 3 months post-stroke (Fig. 3). Furthermore, the duration-MMN amplitude increase correlated with the improvement in the Boston Diagnostic Aphasia Examination test scores from 10 days to 3 months.

Subsequently, as already mentioned, it was found by Särkämö et al. (2010b) that the recovery of the MMNm and behavioural discrimination can be expedited with music and audio-book stimulation. Dividing their 60 middle cerebral artery stroke patients into music and audio-book listening and control groups, these authors recorded patients’ MMNm to frequency and duration changes in a binaurally delivered complex tone. (In addition, all patients received the normal hospital treatment and rehabilitation of stroke patients, of course.) It was found, as expected, that the MMNm amplitudes were, in general, smaller in the lesioned than opposite hemisphere. Importantly, the frequency-MMNm amplitude increased more in both music and audio-book groups than in the control group during the 6-month post-stroke period. In addition, the duration-MMNm amplitude increased more in the audio-book group than in the other groups. Moreover, the frequency-MMNm amplitude changes correlated with the behavioural improvement of verbal memory and focussed attention induced by music listening. The authors interpreted their results as demonstrating that the mere listening to music or speech starting soon post-stroke onset can induce long-term plastic changes in early sensory processing, as reflected by the MMNm 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 rehabilitation of stroke patients in particular in the early post-stroke period.

The deficit of the auditory/language system may be inborn, as is the case in developmental dyslexia, SLI or in the autism spectrum. Because of the high prevalence of these disorders and their devastating effects on the individual’s academic success and thereby self-esteem, early identification and remediation methods should be developed. Recent evidence fortunately shows that the aberrant neural substrate of language deficits can be ameliorated with appropriate intervention. For instance, Pihko et al. (2007) found that language-impaired children at the age of 5–6 years benefited from language and speech exercises. Furthermore, this training also changed the neural processing of speech sounds so that the MMNm for syllable changes became stronger in the left hemisphere.

In dyslexic first-grade children, intervention, judging from an MMNm-amplitude enhancement, induced neural plastic changes and ameliorated reading difficulties (Kujala et al., 2001). These 7-year-old school children were exposed to an audiovisual training programme with no linguistic items (Audilex Program; Karma, 1999) for 7 weeks. Their reading skills as well as the MMNm elicited by tone-order reversals were assessed before and after this training period. After this period, the training group made fewer reading errors and tended to read faster than did the age-matched control group of dyslexic children. Moreover, the MMNm amplitude for tone-order reversals was increased in the training group but not in the control group. These results consequently showed that reading deficits can be ameliorated with audiovisual training and, further, that the improvement of reading skills is associated with plastic neural changes of the central auditory system as reflected by the MMNm enhancement. Furthermore, these positive training results were obtained by using no linguistic stimuli, which suggests that impaired auditory-perceptual processes other than deficient phonology may also contribute to reading impairments. Similar effects were also obtained with extremely low-birthweight children of 6 years of age (Huotilainen et al., 2011). These
children were allocated to a 5-week training programme with Audilex (training group) or to a control group playing computer games. Before and after the intervention, auditory ERPs to sound changes were recorded and reading-related skills were assessed. The MMN responses to frequency and duration deviants increased in amplitude in the Audilex training group but not in the control-game group. However, the reading skills were similar in the two groups after invention and 2 years later.

As already mentioned, the shortening of the abnormally long MMN-peak latency and the MMN-amplitude recovery in drug-resistant adult epilepsy patients after vagus-nerve stimulator implantation was recently found by Borghetti et al. (2007), suggesting a positive effect of vagus-nerve stimulation on central auditory processing in these patients.

Drug-induced improvement. In Table 1, short-term effects of different drugs are reviewed. In addition, in the foregoing, some favourable drug effects in schizophrenia patients were already mentioned (NAC, Lavio et al., 2007; clozapine, Schall et al., 1999; Horton et al., 2011). Moreover, very recently, Dulude et al. (2010) found that nicotine, relative to placebo, not only prolonged the peak latency of the duration MMN but also increased its amplitude in patients to a level comparable with that seen in controls. By contrast, the frequency MMN was not affected. The authors concluded that these preliminary findings demonstrate that acute nicotine can normalise temporal aspects of central auditory processing in patients with schizophrenia, an effect that might be mediated by the activation of α7 nicotinic acetylcholine receptors, the functioning of which is diminished in schizophrenia. The authors further concluded that these ameliorating effects of nicotine may have implications for understanding the increased tobacco smoking in schizophrenic patients and for developing nicotinic pharmacotherapeutics to alleviate sensory-memory impairments in schizophrenia. In addition, a positive effect of nicotine in both smoking and non-smoking normal healthy subjects on temporal–interval processing (indexed by an MMN-amplitude enhancement to ISI deviants) was recently found by Martin et al. (2009).

Furthermore, very recently, it was found by Sawada et al. (2010) that in children of 7–13 years of age with attention deficit hyperactivity disorder (ADHD), the intake of osmotic-release methylphenidate (MPH) increased the MMN amplitude for tone-frequency deviants, which points to the possibility of developing ultrasonic sensory protheses. In a large percentage of those individuals fitted by a CI, CIs are currently the most successful and widely used sensory protheses. In a more detailed study in which subjects were allocated to a 5-week training programme with Audilex (training group) or to a control group playing computer games. Before and after the intervention, auditory ERPs to sound changes were recorded and reading-related skills were assessed. The MMN responses to frequency and duration deviants increased in amplitude in the Audilex training group but not in the control-game group. However, the reading skills were similar in the two groups after invention and 2 years later.

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audible air-conducted sound stimuli and bone-conducted ultrasonic stimuli. Further, when the (40 kHz) ultrasound stimuli modulated by vowels/i/ and /a/ were presented as standards and deviants, respectively, substantial MMNm responses were observed for deviants, indicating that the two sounds were discriminable. Moreover, the equivalent current dipole (ECD) for the MMNm was located within the auditory cortex, in the vicinity of those for deviants, indicating that the two sounds were discriminated by different speech signals. These results provide, according to the authors, the rationale for developing ultrasound hearing aids, which do not require surgery, for those profoundly deaf who can sense ultrasound.

**Improved discrimination in early blind individuals.** A special case of enhanced central auditory function of compensatory nature can be encountered in early blinds. The MMN elicited by sound-location changes was larger in amplitude in early-blind individuals than in sighted control subjects (Kujala et al., 1995a). (The MMN was recorded while subjects' attention was directed to the tactile modality.) This suggests enhanced spatial auditory perception and discrimination in the blind. The result is consistent with behavioural data showing that the blind are more accurate than the sighted in detecting loci of origin of sounds (Lessard et al., 1998; Röder et al., 1999). The scalp topography of MMN response of Kujala et al. (1995a) did not differ between the two groups, however. It, therefore, behaved differently from the N2b (Näätänen et al., 1982; for a review, see Näätänen and Gaillard, 1983) response elicited by auditory targets in an active discrimination condition, which had a scalp topography in the blind that was posterior to that in the sighted (Kujala et al., 1992, 1995a,b). Thus, the MMN appears to be hard-wired in the central auditory system of the blind, reflecting plastic changes within the auditory cortex, whereas the generators of the N2b, associated with attentional processes in audition, may become part of the neural system normally subserving vision. This was supported by imaging studies suggesting occipital activity in the blind during auditory change-detection tasks (Kujala et al., 1995b, 2007, 2000b, 2005b).

**15. Concluding discussion**

This article has shown that central auditory processing, as indexed by the MMN and the MMNm, is affected in a wide range of different clinical conditions and in ageing. Most of these effects are seen as indexing decreased auditory discrimination accuracy. In some cases, however, the duration of auditory short-term sensory memory, essential, for instance, in speech perception and understanding, is affected. This further decreases automatic discrimination when SOAs are prolonged. Moreover, these data also show effects on mechanisms controlling for involuntary shifts of attention (passive attention) or on those determining the characteristics of backward masking in different patient groups.

Consequently, this article has shown that the MMN provides a unique window to the neuropsychology of central auditory processing, and hence a possibility for the objective assessment of auditory discrimination and sensory memory, in different patient groups, which previously could be mainly inferred from behavioural performance only. This is a major improvement, in particular when considering the special communicational and motivational problems with patients, deducing from the reliability of the results, and the fact that reliable behavioural measurements are not at all possible in some clinical groups and often in small infants. These new possibilities in particular involve the improved monitoring of the patient's state and the prediction of its future development, for example, the prediction of coma or PVS outcome and even that of the extent of the cognitive recovery of these patients (during the next 2 years; Wijnen et al., 2007), or the monitoring of, and predicting, the progress of schizophrenia. Moreover, importantly, very recent results of Bodatsch et al. (2011) showed that the duration MMN can predict, in individuals in schizophrenia-risk group, conversion to first-episode schizophrenia and even when this would occur in the period of 2 years. In addition, another recent study (Banati and Hickie, 2009) suggested that the duration and frequency MMNs might enable one to online monitor local disease activity and neuronal death in patients with schizophrenia.

Furthermore, in case of schizophrenia (see Lavoie et al., 2007; Horton et al., 2011; Javitt et al., 2008; Banati and Hickie, 2009; see also Berk et al., 2008a,b), and perhaps of other severe neuropsychiatric, neurological and neurodevelopmental disorders, too, the MMN can be used as an online index of treatment efficacy. As far as dyslexia is concerned, such a use of the MMN in assessing the effectiveness of different rehabilitation programmes is already well established (Kujala et al., 2001). In addition, in the foregoing, we reviewed results of Särkämö et al. (2010a) demonstrating how the MMNm can be used in evaluating the effectiveness of different auditory stimulus material in an attempt at facilitating stroke recovery.

Some further clinically important uses of MMN data are, among other things, the possibility to determine the dyslexia risk in newborns and infants (Maurer et al., 2003; Leppänen et al., 2002; van Leeuwen et al., 2006; Friedrich et al., 2004), the magnitude of cognitive and functional deficit associated with different clinical conditions (Näätänen et al., 2011a) and the degree of severity of different conditions (in Schizophrenia: Umbricht et al., 2006; Devrim-Ucok et al., 2008; Todd et al., 2008; Light and Braff, 2005a,b; Salisbury et al., 2002, 2007; Stuttering: Corbera et al., 2005; PTSD: Menning et al., 2008; Cleft Palate: Ceponiene et al., 1999, 2000, 2002; Stroke and Aphasia: Ivonen et al., 2003; Pettigrew et al., 2005; Särkämö et al., 2010b; Dyslexia: Baldeweg et al., 1999; Kujala et al., 2001).

One might wonder why auditory discrimination is affected in such a large number of different clinical conditions (Table 1), which indeed points to a possible common pathology shared by these different conditions. A major part of this common pathology appears to be found in the deficient functioning of the NMDAR system, as there is very strong evidence indicating that MMN deficiency reflects deficient NMDAR functioning (Javitt et al., 1996; Näätänen et al., 2011a). For example, sub-anaesthetic doses of ketamine, an NMDAR antagonist, attenuated the MMN amplitude of healthy volunteers (Kreitschmann-Andermahr et al., 2001: MMN; Umbricht et al., 2000, 2002), monkey (Javitt et al., 1996), rat (Tikhonravov et al., 2008, 2010) and mouse (Ehrlichman et al., 2002), and caused schizophrenic kinds of psychotic experiences in normal subjects (Umbricht et al., 2000, 2002; see also Sauer and Volz, 2000; Pang and Fowler, 1999). Furthermore, ketamine disturbed the performance in a memory task in normal subjects in a manner similar to that normally observed in schizophrenia, as shown by Umbricht et al. (2000). Importantly, it was found by Umbricht et al. (2002) that the smaller was the subject's MMN amplitude for frequency and duration changes before ketamine administration, the stronger were the psychotic experiences caused by the drug. Therefore, the authors concluded that the MMN in the normal state of consciousness indexes the vulnerability to disruption of the NMDAR system in normal healthy subjects. Consequently, the MMN appears to index the functional state of the NMDAR-mediated neurotransmission even in subjects demonstrating no psychopathology and may therefore “become a useful tool in studies on NMDAR functioning in humans” (Umbricht et al., 2002).
Consequently, the MMN attenuation observed in a large number of different clinical populations and conditions (Table 1) can, to a large extent, be accounted for by NMDAR dysfunction associated with different clinical conditions. For instance, as already reviewed, the dysfunction of the NMDAR system plays a central role in the brain pathology of schizophrenia and in particular in the cognitive deficit in these patients (Javitt et al., 1996; Coyle et al., 2006). Moreover, the cognitive decline occurring in several other neurocognitive abnormalities might also be accounted for, at least in part, by the dysfunctional NMDAR system (Nätänen et al., 2011a). Alzheimer’s disease, stroke, traumatic brain injury and even normal ageing are accompanied by widespread dysfunctions in the NMDAR system (Lipton and Rosenberg, 1994; Magnusson et al., 2010; Biegon et al., 2004; Dalkara et al., 1996; Izquierdo, 1991; McGeer and McGeer, 2010). For example, Dhawan et al. (2010) recently found that middle central artery occlusion in rats resulted in widespread decreases in NMDAR density in brain regions extending far beyond the infarct area, including even regions contralateral to the lesion important to cognitive function. Dhawan et al. (2010), therefore, concluded that a persistent and widespread loss of NMDARs may contribute to cognitive and other neurological deficits in stroke patients, which cannot be localised to the side of infarction.

Importantly, this NMDAR functional deficiency may hence account for, besides decreased discrimination accuracy, even the cognitive and functional decline occurring in a number of these conditions (Table 8) (for a review, see Nätänen et al., 2011a). It is, for instance, well established that the adequate functioning of the NMDAR system plays a crucial role in the initiation of long- and working memories (Javitt et al., 1996; Newcomer et al., 1998). Therefore, the MMN and MMNm deficiency reflecting a deficient NMDAR function can also index cognition and its decrement in ageing and in different neurological and neuropsychiatric abnormalities (Nätänen et al., 2011a). Consequently, as an easily accessible non-invasive measure of the functional condition of the NMDAR system, the MMN (MMNm) might play an important role in future attempts at understanding what is common in the different neuropsychiatric diseases and abnormalities and what is specific to each of them (Umbricht et al., 2003). These conclusions are further supported by studies showing that pharmacological manipulations enhancing cognition also enhance the MMN (MMNm) response (Baldeweg et al., 2006; Dunbar et al., 2007; Inami et al., 2005; Fisher et al., 2010; Harkrider and Hedrick, 2005; Engelnd et al., 2002; Knott et al., 2006, 2009) and vice versa (Pang and Fowler, 1999; Nakagome et al., 1998; Serra et al., 1996; Jääskeläinen et al., 1996a), and, further, that the MMN-cognition relationship holds even in normal adults (Light et al., 2007; Bazana and Stelmack, 2002; Beauchamp and Stelmack, 2007; Troche et al., 2009, 2010) and children (Liu et al., 2007).

Optimising MMN protocols for clinical environments. Perhaps the most frequent issues associated with use of the MMN in clinical environments is time required to record enough data to obtain an identifiable response and the expertise required to identify when a response is present or absent. By definition, the traditional MMN protocol is very time consuming to obtain information when a response is present or absent. By definition, the traditional MMN protocol is very time consuming to obtain information about the existence of a single stimulus contrast. In a standard paradigm, the standard stimulus is presented 80–90% of the time, with deviant stimulus presentations, which evoke the MMN, randomly interspersed through the sequence. The introduction of the multiple-deviant paradigm for tones (Nätänen et al., 2004; Pakarinen et al., 2007, 2010; Fisher et al., 2011; Grimm et al., 2008; Jankowiak and Berti, 2007; see also Vaz Pato et al., 2002; Deacon et al., 1998) and for speech (Pettigrew et al., 2004b; Pakarinen et al., 2009; Sorokin et al., 2010; Lovio et al., 2009) and music (Vuust et al., 2011) provided a method for rapidly acquiring information on the number of stimulus contrasts. This approach considerably increases the amount of information that can be gathered within a specific time period. Equally as important are methods that would further reduce the amount of time required to acquire sufficient data that reach some objective criteria of identification.

One such approach has recently been described by Rahne et al. (2008). In this modification to standard averaging, individual epochs to stimulus presentation are sorted on the signal-to-noise ratio (SNR) to each individual epoch. This epoch with the highest SNR, that is, the lowest background noise, is added first to average. Individual epochs are then added to the average in rank order based on the background noise in each epoch. Thus, averaging is continued until the SNR is optimised. Objective or statistical detection of these responses could then easily be achieved by using one of a number of online algorithms involving randomisation or bootstrapping analyses such as those proposed by, for example, Ponton et al. (1997) or Fujioka et al. (2005). Moreover, further progress to this end has been very recently made by Cong et al., 2009, 2010, 2011; Burger et al. (2007); Kalyakin et al. (2007, 2008a,b, 2009) and Marco-Pallares et al. (2005).

Needless to say, a lot of work is still needed to bring the MMN methodology to clinics as a tool of everyday patient work in which reliable measurements have to be carried out at the level of individual patients (Bishop and McArthur, 2004; Boly et al., 2011; Taylor and Baldeuweg, 2002; Lang et al., 1995), but studies as those reviewed in the foregoing have shown that this goal is both valuable and probably also attainable.

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