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COMT Val$^{108/158}$Met genotype modulates human sensory gating

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ABSTRACT

Background: The catechol-O-methyltransferase (COMT) Val$^{108/158}$Met polymorphism of the dopamine system is essential for prefrontal cortex processing capacity and efficiency. In addition, dopaminergic neurotransmission is also associated with the sensory gating phenomenon protecting the cerebral cortex from information overload. It is however unclear if COMT genotype as a predictor of prefrontal efficiency modulates sensory gating on the level of the auditory cortex, i.e. the gating of the auditory evoked P50 and N100 components.

Methods: P50 and N100 gating and COMT Val$^{108/158}$Met genotype were determined in 282 healthy subjects of German descent carefully screened for psychiatric or neurological disorders.

Results: A significant effect of the COMT genotype was observed for N100 gating ($F=4.510$, $df=2$, $p=0.012$) but not for P50 gating ($F=0.376$, $df=2$, $p=0.687$). Contrast analysis showed that Met/Met individuals had poorer N100 gating compared to Val/Met ($F=-12.931$, $p=0.003$) and the Val/Val individuals ($F=-11.056$, $p=0.057$).

Conclusion: The results indicate that a high prefrontal efficiency as suggested by the COMT Met/Met genotype is associated with to a poor sensory gating of the N100 component. This would fit in a model where a high prefrontal processing capacity allows a pronounced afferent input of sensory information from the auditory cortex as reflected by a poor sensory gating. The more pronounced prefrontal contribution to the N100 compared to the P50 component may explain the exclusive genotype association with the N100 sensory gating. This preliminary model should be replicated and validated in future investigations.

Introduction

Sensory gating, a core feature of information processing is suggested to be a filter mechanism protecting the central nervous system from sensory overload (McGhie and Chapman, 1961; Braff et al., 1992; Boutros et al., 2004). In this concept, the cerebral response to a repeated identical stimulus is inhibited, which is mediated by pre-attentional habituation to irrelevant sensory input. Therefore, humans are able to differentiate between important and unwanted sensory information and thereby to adapt rapidly to different contextual situations (Fruhstorfer et al., 1970; Braff and Geyer, 1990; Freedman et al., 1991; Grunwald et al., 2003; Potter et al., 2006). A disturbed sensory gating function may cause inadequate sensory information processing and results in a flooding of higher cortical areas with irrelevant information (Boutros et al., 2004). This was implicated as a pathobiological mechanism in severe disturbances of perception, emotion and behaviour (Freedman et al., 1991; McDowd et al., 1993; Kumari et al., 2008) and is one of the most robust biological findings in schizophrenia (Siegel et al., 1984; Baker et al., 1987; Braff and Geyer, 1990; Braff et al., 1992; Bramon et al., 2004) and among other psychiatric disorders (Franks et al., 1983; Lijffijt et al., 2009b).

Sensory gating deficits in schizophrenia and other psychiatric disorders were primarily investigated for the auditory evoked P50 and N100 component (Adler et al., 1982; Freedman et al., 1991; Boutros et al., 1993). The P50 is probably the earliest component—about 50 ms after stimulus onset—of the auditory evoked potential that represents sensory gating (Grunwald et al., 2003). The somewhat later N100 potential is known to be the largest mid-latency component of the auditory evoked potentials with a peak between 80 and 120 ms after the presentation of an acoustic stimulus (Spreng, 1980; Gallinat et al., 2002). In comparison to the P50 component, it might be more influenced by arousal and was associated with early attentional processing (Nash and Williams, 1982; Putnam and Roth, 1987; Young

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et al., 2001; Gallinat et al., 2003). A decreased degree of suppression of the N100 is a relatively stable physiological abnormality in subjects suffering from schizophrenia, though the N100 has not been studied as intensively as the P50 (Strik et al., 1992; Frodl et al., 1998; Laurent et al., 1999; Brockhaus-Dumke et al., 2008).

However, neither the neurophysiological mechanism underlying sensory gating nor the exact anatomical locus of its generation have yet been fully identified. Indirect evidence has been gained by lesion studies indicating an association of deficits in auditory response inhibition with lateral prefrontal cortex (Knight et al., 1999). Studies on patients suffering from temporal lobe epilepsy showed reduced P50 gating; suggesting that anatomical structures mediating P50 gating might be located in temporal structures (Weate et al., 1995). In rat brains, the response of hippocampal pyramidal interneurons, to the second stimulus was found to be almost completely suppressed above all in the CA3 region, indicating that the hippocampus might be an essential mediator of sensory gating (Bickford-Wimer et al., 1990; Freedman et al., 1996). In studies employing magnetencephalography (MEG), a method with high spatial resolution, the M50 was localized in the auditory cortex of the superior temporal gyrus but also to several sources in the frontal lobes (Garcia-Rill et al., 2008; Thoma et al., 2008; Weiland et al., 2008).

Regarding its neurochemical bases, different systems of neurotransmitters have been suggested to be involved as mediators of sensory gating (Laruelle et al., 2003). Most of the findings in this field have been achieved by animal studies in mice, rats and rodents, formerly by administering specific psychotropic drugs and measuring the effect on sensory gating (Geyer et al., 2001; Swerdlow et al., 2006). Amphetamine is known to augment intrasynaptic dopamine concentrations by amplifying its release and inhibiting the reuptake. Its application to healthy humans was associated with a disrupted suppression of the P50 (Adler et al., 1986; Light et al., 1999). This effect was reversible when dopamine receptor (D2) antagonists like haloperidol was administered. Typical antipsychotics as haloperidol and flupenthixol might ameliorate poor sensory gating in drug-free subjects (Adler et al., 1986; Csomor et al., 2008). Other hypotheses suggest different synergic constellations of neurotransmitters as a base of functioning sensory gating, e.g. serotonin and dopamine (Mann et al., 2008), or monoamine inhibition and nicotine antagonism (Siegel et al., 2005).

The catechol-O-methyltransferase (COMT) is one of the major enzymes that methylate the catecholamine's dopamine, norepinephrine and epinephrine to homovanillic acid especially in the prefrontal cortex (Karoum et al., 1994; Gogos et al., 1998). An intensively studied single nucleotide polymorphism (SNP)($Val^{108/158}$Met) of the COMT gene has been suggested to predict executive cognition (Goldberg et al., 2003) and the efficiency of prefrontal functions in humans (Egan et al., 2001; Gallinat et al., 2003; Winterer et al., 2006). At the q11 band of chromosome 22 in humans, valine (val) is replaced by methionine (met), thus diminishing dopamine methylation 3 or 4 times (Gogos et al., 1998), leading to increased prefrontal dopamine concentrations.

Due to the previously observed effects of the dopaminergic neurotransmission on sensory gating as investigated with pharmacological challenges, the objective of our work was to study whether the COMT $Val^{108/158}$Met polymorphism is associated with the most common investigated surrogate parameters of sensory gating, the auditory evoked P50 and N100 component. The P50 and to a lesser degree the N100 sensory gating represent intermediate phenotypes because of underlying genetic factors (Siegel et al., 1984; Waldo et al., 1988; Turetsky et al., 2008) associating with diseases e.g. schizophrenia (Bramon et al., 2004), co-segregation with schizophrenia within families (Clementz et al., 1998a,b); Siegel et al., 1984; Waldo et al., 1992) and sufficient test-retest-reliability (Boutros et al., 1991; Rentzsch et al., 2008a). We studied sensory gating of the P50 and N100 component in a large sample of 282 healthy subjects carefully screened for mental disorders.

Methods and materials

Subject ascertainment

The study was approved by the ethics committee of the Charité—Universitätsmedizin Berlin. All subjects gave written, informed consent. Subjects were recruited by newspaper advertisements and were renumerated for their participation. After initial screening by telephone interview using a structured questionnaire, subjects were examined by a staff psychiatrist using a widely acknowledged structured interview (M.I.N.I., Sheehan et al., 1998). Exclusion criteria were any Axis I or Axis II disorders following DSM-IV. Furthermore, hearing disorders, significant cardiovascular, hepatic, renal, gastrointestinal, metabolic, or other systemic disease, concurrent neurological illness, organic mental disorder, seizure disorder, mental retardation, Parkinson's disease, migraine, ischemic brain insults, non-compensated hypothyroidism or diabetes mellitus were detected and led to exclusion. None of the subjects reported a family history of schizophrenia or schizoaffective disease.

P50 and N100 recording

Subjects were seated in a sound-attenuated and electrically shielded room adjacent to the recording apparatus (Neuroscan SynAmps model 5083, El Paso, TX), with closed eyes, in a slightly reclined chair with a headrest. Auditory stimuli consisted of 175 identical pairs of clicks generated by a PC-stimulator with “Creative Labs SoundBlaster 16”-soundcard (duration: 1 ms square wave, 109 dB1) through calibrated headphones. Paired clicks were separated by 500 ms. Four different fixed inter-pair intervals were used in a pseudo-randomized order (1.5 s, 3 s, 3.8 s, and 4.6; mean inter-pair interval: 2.8 s) (Rentzsch et al., 2008b). The responses evoked by clicks were recorded with 29 tin electrodes referred to Cz, using an electrode cap following the International 10/20 System with additional electrodes. Fpz served as ground. Eye movements were recorded across an electrode placed 1 cm laterally to the left eye (EOG). Electrode impedance was less than 10 kΩ. Data were collected at a sampling rate of 500 Hz (gain 5000; analog band pass filter: 0.15–100 Hz). The EEG measures were taken by different, specially trained investigators.

Parameterization and peak definition

The EEG was analyzed offline using “Brain vision analyzer” software (Version 1.1, Brain vision, Munich, Germany). The data were digitally filtered (P50: high-pass 10 Hz, 24 dB octave; N100 and P200: high-pass 0.5 Hz, 24 dB octave) after re-referencing to average reference, segmentation (350 ms pre-first-stimulus to 800 ms post-stimulus), artefact rejection (i.e. exclusion of segments showing activity greater/lower than 100 μV in any of the 29 channels and/or in the EOG at any point of the sweep period; no further blink correction algorithm was applied) and baseline-correction. After averaging the remaining sweeps, latencies and amplitudes of the P30, N40, P50, and N100 at the Cz electrode were analyzed on the basis of automatic peak detection in combination with a visual control. All subjects had more than the minimum of 90 segments per average. The P50 component was defined as the most positive response between 40 and 80 ms post-stimulus preceeded by a P30 wave in a 20–50 ms range. If there was no identifiable P30, the most prominent positive component in the P50 time range was used as P50. The N100 component was defined as the most negative deflection in the range of 60–170 ms post-stimulus. All amplitudes were measured in relation to the N40 peak, which served as a baseline (peak-to-peak; referred to as N40–P50, N40–N100). N40 was defined as the most prominent negative peak between P30 and P50. Whenever these were equivocal, the most negative peak preceding the P50 was used as N40. When no