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Attention network test (ANT) reveals gender-specific alterations of executive function in schizophrenia

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Abstract

The Attention Network Test (ANT) provides measures for three different components of visual attention: executive control (=conflict inhibition), orienting, and alerting. There is reasonable evidence that alterations of attention—mainly in the executive/conflict domain—are associated with susceptibility to psychiatric illness. Specific impairments may be a characteristic for a medical condition such as schizophrenia and thus shift our understanding from a neuropsychological endophenotype to a more precise genetic understanding of this disorder. Study subjects comprised 35 schizophrenic patients and 35 healthy controls (13 female and 22 male in both groups). The ANT was administered to all participants and rated individual responses for the three factors (alerting, orienting, and conflict) and their respective ratios relative to mean reaction times. With regard to gender differences, group comparisons were performed for schizophrenic patients vs. healthy controls. Significant differences between patients and controls could be detected for mean reaction time (639 vs. 538 ms) and for conflict ratio (0.158 vs. 0.191). The latter difference mainly resulted from gender-specific variances of the conflict network in opposite directions. The executive function as represented by the conflict network of visual attention of the ANT is affected in schizophrenia. We have detected hitherto unreported gender-specific differences between healthy controls and schizophrenic patients. Especially as regards the conflict network, the ANT offers a promising methodology to detect a neuropsychological endophenotype of schizophrenia.

Keywords: Visual attention; Neurocognitive test; Conflict ratio; Endophenotype

1. Introduction

Visual attention may be regarded as an integrated brain function combining three different specialised networks: the alerting network, the orienting network, and the executive control network (Posner and Petersen, 1990). The alerting network can effectuate a wakeful state to prepare for sensory input. The orienting network can focus attention on relevant sources of expected sensory input. The executive network (=conflict network) is involved in complex decision making and error monitoring.

The Attention Network Test (ANT) is a neurocognitive test that was developed to provide a separate measure for these three different components of visual

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attention. Validation data in a healthy population showed sufficient independence of the three networks and generated reliable single-subject estimates of alerting, orienting, and executive function (Fan et al., 2002). A twin study yielded evidence for heritability of the measured variables, with the exception of the orienting effect (Fan et al., 2001). With an adapted version of the ANT, the development of attentional networks during childhood was investigated (Rueda et al., 2004), indicating that reaction time, alerting, and accuracy improved with age, executive function remained stable after the age of seven, and orienting was not influenced by age. In healthy adults activation patterns in neuroimaging studies showed specific anatomical locations of the three networks in the human brain (Fan et al., 2005; Kincade et al., 2005; Thiel et al., 2004). Genetic studies revealed associations of polymorphisms in candidate genes for psychiatric diseases (dopamine D4 receptor (DRD4), dopamine transporter (DAT), catechol-*O*-methyl transferase (COMT), monoamine oxidase A (MAOA) and tryptophan hydroxylase 2 (TPH2)) with visual attention, and activation in the anterior cingulate cortex (ACC) (Fan et al., 2003; Fossella et al., 2002; Opgen-Rhein et al., 2008; Reuter et al., 2007). Wang et al. (2005) administered the ANT to a group of Chinese schizophrenic patients and healthy controls, demonstrating large and highly significant differences in the executive network and smaller but significant differences in the orienting network. Gooding et al. (2006) confirmed these findings, showing that schizophrenia-spectrum patients take longer on average to resolve conflict. Our group found lower ACC activity during resolution of conflict in schizophrenic patients (Neuhaus et al., 2007), and Nestor et al. (2007) found differences in the alerting and in the orienting network. Moreover, other neurocognitive tasks, also measuring reaction time as a function of stimulus conflict in schizophrenia-spectrum patients, contributed substantially to this field of research recently (Guillaume et al., 2007; Steel et al., 2007).

Schizophrenia today is mainly viewed as a neurodevelopmental disorder (Cannon et al., 1999; Lewis and Levitt, 2002), leading to subsequent alterations of brain morphology (Andreasen et al., 1990; Antonova et al., 2005; Cannon and Marco, 1994) and function (Aleman et al., 1999; Barch et al., 2001; Caspi et al., 2003). Defective neuronal development is likely to be evoked by complex polygenetic constellations, and some promising candidate genes increasing susceptibility for schizophrenia have been found (Harrison and Weinberger, 2005). Therefore a different perspective on the disorder has been proposed: to define the phenotype on the basis of abnormalities in neural circuits and in fundamental cognitive processes (Andreasen, 2000). Pursuing the plan to identify such a phenotype, the detection of a well-defined neuropsychological endophenotype could amalgamate genetic susceptibility and cognitive impairments (Cornblatt and Malhotra, 2001; Gottesman and Gould, 2003). By applying the ANT to schizophrenia patients we aimed at detecting specific alterations that might serve as a potential endophenotype for schizophrenia. We expected to find differences mainly in the executive network, as alterations in this domain have been described in schizophrenia consistently (Heinrichs and Zakzanis, 1998; Hutton et al., 1998; Wolf et al., 2002). Moreover, we wanted to look for possible influencing factors for the expected performance variations. Taking into account that a recent study of a large population-based sample indicated a substantial influence of gender and free testosterone on cognitive performance (Thilers et al., 2006), and that many researchers reported—albeit often ambiguous—influences of gender on cognitive performance (Hoff and Kremen, 2002), we planned to examine gender differences in our sample.

2. Methods

2.1. Subjects

Thirty-five Caucasian schizophrenic inpatients (13 female, 22 male) participated in this study. Two trained psychiatrists confirmed their diagnoses by the Structured Clinical Interviews for DSM-IV-TR Axis I Disorders (First et al., 2002) and for DSM-IV Personality Disorders (First et al., 1997) independently, and rated patients on the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Patients neither had other axis I (including substance abuse other than smoking tobacco) or axis II diagnoses, nor did they suffer from any neurological diseases. All patients were clinically stable, received atypical antipsychotic medication, and did not suffer from extrapyramidal motoric side effects as assessed by the Simpson–Angus Scale (Simpson and Angus, 1970) and the Abnormal Involuntary Movement Scale (Guy, 1976). 35 Caucasian controls (13 female, 22 male) were recruited from newspaper advertisements and proved healthy after screening with the M.I.N.I.[1] (Sheehan et al., 1998). All participants had normal or corrected-to-normal vision. Descriptive statistics are displayed in Table 1. The study was performed in agreement with the 1964 declaration of Helsinki and its subsequent amendments, the design was approved by the ethics committee of the Free

[1] M.I.N.I. = **M**ini-**I**nternational **N**europsychiatric **I**nterview.