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Neuropsychological functioning in young subjects with generalized anxiety disorder with and without pharmacotherapy

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ABSTRACT

The purpose of this study was to investigate the neuropsychological functioning and the effect of antidepressant drug intake on cognitive performance in a group of relatively young generalized anxiety disorder (GAD) patients. Forty patients with a DSM-IV diagnosis of GAD and 31 healthy subjects participated in the study (Control group, CON). None of the selected subjects had comorbid depression.

GAD subjects were divided into two different subgroups: 18 were taking antidepressants [GAD-pharmacotherapy (GAD-p group)] and 22 were treatment-naïve (GAD group). Each group was administered with a comprehensive neuropsychological battery to assess attention, memory and executive functions.

Performance on executive and non-verbal memory tasks of both GAD groups was largely worse than the CON group. However, these deficits seem to be more marked in patients taking antidepressants, especially in the domains of attention, non-verbal memory and executive functions.

The present study indicates that GAD is associated with cognitive impairments among young adults. However, the observed association of neuropsychological deficits and the use of pharmacotherapy suggest a possible effect of antidepressant treatment on attention, executive functioning and non-verbal memory.

1. Introduction

Generalized anxiety disorder is a persistent and common disorder, in which the patient has unfocused worry and anxiety that is not connected to recent stressful events, although it can be aggravated by certain situations (Tyrer and Baldwin, 2006). The incidence of this disorder in men is half that in women (Slade and Andrews, 2001) and is lower in older people (Gale and Davidson, 2007). GAD is characterized by feelings of threat, restlessness, irritability, sleep disturbance, and tension, and symptoms such as palpitations, dry mouth, and sweating. In fact, as with other anxiety disorders, GAD is associated with impairment in daily life functioning (Ezpeleta et al., 2001) and predicts high risk for future problems (Kessler et al., 2008).

The majority of the research reported that any type of anxiety disorders, including panic disorder, obsessive compulsive disorder, social phobia, and post-traumatic stress disorder has detrimental effects on neuropsychological performance, such as executive function, memory, attention, and learning (Asmundson et al., 1995; de Geus et al., 2007; Harkin and Kessler, 2011; Ludewig et al., 2003; Mantella et al., 2007; McNally, 2006; Polak et al., 2013; Tempesta et al., 2012; Toren et al., 2000). However, despite a large amount of research evaluating the neuropsychological performance in anxiety disorders only few studies have focused specifically on GAD. Research focusing on cognitive functioning demonstrated memory impairments in elderly subjects with GAD (Mantella et al., 2007). A recent study also showed worse performance in older subjects with GAD compared to a control group on measures of information processing speed, working memory, inhibition and problem-solving as well as immediate and delayed memory (Butters et al., 2011). On the other hand, the only two studies (Airaksinen et al., 2005; Castaneda et al., 2011) on small samples of young subjects with GAD did not show any cognitive dysfunction.

This disorder typically appears during the mid-adolescent years (Maslowsky et al., 2010; Rickwood and Bradford, 2012) and is unremitting throughout life if not properly treated.

Two comparably effective treatments for GAD are cognitive behavioral therapy (CBT) (Scott et al., 2005) and selective serotonin reuptake inhibitor (SSRI) (Birmaher et al., 2003). However, even if antidepressants have demonstrated efficacy in GAD treatment, the

Abbreviations: GAD, Generalized anxiety disorder; CON, Control group; GAD-p group, GAD-pharmacotherapy; GAD group, Generalized anxiety disorder group; CBT, cognitive behavioral therapy; SSRI, selective serotonin reuptake inhibitor; SCID-P, Structured Clinical Interview for DSM-IV-Patient Edition; STAI, State-Trait Anxiety Inventory; BDI, Beck Depression Inventory; PSQI, Pittsburgh Sleep Quality Index; TAS-20, Toronto Alexithymia Scale; CBTT, Corsi Block Tapping Test; LCT, Letter Cancellation Task; CMT, Cognitive Map Test; WCST, Wisconsin Card Sorting Test; ROCF, Rey–Osterrieth Complex Figure Test.

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cognitive changes that accompany the clinical improvement noted with this treatment are unclear.

Cognitive (memory) impairment associated with SSRI use has been suggested (Goodnick and Goldstein, 1998; Joss et al., 2003; Wadsworth et al., 2005), but the findings are contradictory. Both beneficial (Levkovitz et al., 2002; Harmer et al., 2004; Zobel et al., 2004) and detrimental (Joss et al., 2003; Masand and Gupta, 1999; Schmitt et al., 2001; Wadsworth et al., 2005) effects have been indeed reported. For example, Zobel et al. (2004) reported improvements in both working and episodic memory following 4 weeks of antidepressant treatment. Instead, Wadsworth et al. (2005) when investigating cognitive functions in a working sample showed that SSRI use was associated with memory impairment, specifically poorer episodic memory. In this study we carried out a neuropsychological evaluation, during the antidepressant treatment, in a group of young subjects with GAD. We also compared these participants [GAD-pharmacotherapy (GAD-p group)] with a group of drug-naïve young subjects with GAD (GAD group) and with a group of healthy young subjects [Control group (CON group)], to identify any cognitive changes related to pharmacotherapy of anxiety.

Given that worry takes up cognitive capacity and leaves less attentional resources for the tasks at hand (Butters et al., 2011), we hypothesized that the GAD group would perform worse than the control group, regardless of the pharmacotherapy treatment. Moreover, given that selective serotonin inhibitors have repeatedly been shown to impair performance in sustained attention tasks (Wingen et al., 2007) we hypothesized that the GAD group during pharmacotherapy may show a further deterioration of cognitive performance compared to the other groups, particularly on measures of attention and executive functions.

2. Material and methods

2.1. Participants

Forty subjects between 20 and 35 years with first episode of GAD were recruited at the outpatient facility of Psychiatric Service of Diagnosis and Treatment, Hospital G. Mazzini, ASL 4, Teramo and considered eligible for this study. A diagnosis of GAD was determined by experienced clinicians who had completed the diagnostic assessment based on the Structured Clinical Interview for DSM-IV-Patient Edition (SCID-P) (First et al., 1995). In our sample, the inter-rater reliability was 0.78. We selected only the patients that received a primary diagnosis of generalized anxiety disorder (GAD). Comorbid axis I disorders were considered as an exclusion criterion. In addition, GAD patients were included in the analyses if they did not display current or past major depression, current or past manic or hypomanic episode, comorbidity with schizophrenia or other psychotic disorders, comorbidity with any eating disorder, history or current drug or alcohol dependence, or mental retardation. No patient had ever received an evidence-based structured psychotherapy.

The group of subjects with anxiety disorder ($n = 40$) was divided into two different groups. The first group comprised 18 subjects (10 female and 8 male; mean age: 32.66 ± 7.49 years) diagnosed with generalized anxiety disorder during pharmacotherapy (GAD-p group; 10/18 escitalopram, dose mean: 14 mg/day, 8/18 venlafaxine, dose mean: 178 mg/day).

The second group comprised 22 drug-naïve young subjects (14 female and 8 male; mean age: 30.44 ± 7.50 years) with a diagnosis of generalized anxiety disorder (GAD group).

The mean duration of diagnosis of GAD group was 7.9 ± 2.6 months (median 8.0), whereas in GAD-p was 7.4 ± 2.4 months (median 7.5).

Based on a clinical interview (Schedule 4 of Cognitive Behavioural Assessment 2.0), we selected 31 healthy control subjects (21 female and 10 males; mean age: 32.66 ± 7.49 years) ascertaining that they did not suffer from neurological, psychiatric, or any other serious medical condition. In addition, we excluded from the control group the subjects with alexithymia, measured by the Toronto Alexithymia Scale (TAS-20 scores ≥ 51; Bagby et al., 1994) and sleep disorders, evaluated by the Pittsburgh Sleep Quality Index (PSQI scores ≥ 5; Buysse et al., 1989).

None of the participants in the control group were taking psychopharmacological drugs.

They consisted of university students and workers.

Written informed consent was obtained from each participant before the study began.

2.2. Clinical evaluation

The clinical evaluation was conducted individually by one psychologist (M.M.) through the following instruments: the State-Trait Anxiety Inventory (STAI, Spielberger and Vagg, 1984; Italian validation: Moroni et al., 2006); the Beck Depression Inventory (BDI: Beck et al., 2009); the Pittsburgh Sleep Quality Index (PSQI: Buysse et al., 1989) and the Toronto Alexithymia Scale (TAS-20: Bagby et al., 1994).

The STAI measures both trait (T) and state (S) anxiety. Trait anxiety is assumed as a predisposition to perceive situations as potentially threatening, possibly leading to an increase in state anxiety. Both the state and trait sections of this questionnaire comprise 20 questions, with a total score ranging from 0 to 60. Both scales have shown good psychometric qualities (Cronbach α: STAI-S 5 0.92; STAI-T 5 0.91; Moroni et al., 2006). The normative scores (mean ± standard deviation (SD)) in the 20–35 years age range are as follows: males STAI-S: 38.0 (9.2), STAI-T: 36.9 (9.1); females STAI-S: 40.9 (10.1); STAI-T: 40.4 (10.6).

The Beck Depression Inventory (BDI) is a multiple-choice self-report inventory assessing depressive symptoms in adults (Beck et al., 1961). The cut-off score for depression is usually set above 11.

The Pittsburgh Sleep Quality Index (PSQI: Buysse et al., 1989) consists of 19 questions assessing a wide variety of factors relating to sleep quality in the preceding month (estimates of sleep duration and latency and of the frequency and severity of specific sleep-related problems). A global score >5 is considered as an indicator of relevant sleep disturbances (Buysse et al., 1989).

Table 1 shows the scores to the above tests, separately for the three groups. The subjects of GAD disorder (GAD-p group and GAD group) reported significantly higher scores than controls to all the considered scales. However, none of these participants had comorbid depression or other psychiatric disorders.

2.3. Neuropsychological tests

The neuropsychological test battery, including internationally used, validated test methods administered in a fixed order, was selected to allow the comparison of short-term memory, visuospatial memory, a person's proneness to committing cognitive errors, attention and executive functions between the study samples. Tests were administered and scored following standardized procedures by one psychologist (M.N.) blind to the diagnosis.

All tests were administered according to the standard instructions and the subjects took approximately 90 min to complete the battery.

Working memory was measured with the *Digit Span* (based on the WAIS-III subtest, Wechsler, 1981). In this simple task, the subject has to repeat a sequence of numbers in the order and in the reverse order in which the numbers were stated by the experimenter. The span is increased by one digit for each successful trial. The test is terminated when a participant either fails to reproduce the correct sequence for two consecutive strings with the same number of digits or the final nine-digit number sequence is successfully reproduced. Participants receive two points for each successful digit sequence reproduction if correct on the first attempt, or one point if correct on the second