Antidepressive therapy with escitalopram improves mood, cognitive symptoms, and identity memory for angry faces in elderly depressed patients

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Originally published at:
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Abstract

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Abstract
Depression is a common disorder in the elderly handicapping patients with affective and cognitive symptoms. Because of their good tolerability relative to the older tricyclic compounds, selective serotonin reuptake inhibitors (SSRIs) are increasingly used for the treatment of depression in the elderly. Little is known about their effects on cognition in elderly patients. In the present 4-wk, single-centre, randomized, open-label trial we investigated the antidepressive effects of escitalopram, an SSRI, in 18 elderly depressed patients [mean age (± S.E.M.) 76.2 ± 1.8 yr] compared to 22 healthy age-matched controls (mean age 76.9 ± 1.8 yr). Affective and cognitive symptoms were assessed using the Geriatric Depression Scale (GDS), Mini-Mental State Examination (MMSE), and a face portrait recognition test to assess memory for happy and angry faces. Depressed patients prior to treatment had markedly reduced memory performance. Treatment with escitalopram improved affective and cognitive symptoms significantly. Furthermore, escitalopram treatment improved memory for negative facial stimuli. Control subjects confirmed the well-established memory bias favouring recognition of identities acquired with happy expressions. Importantly, this bias was absent in depressed patients prior to, but also after treatment. In conclusion, escitalopram, even after a relatively short treatment period, was effective in treating depression in the elderly and may help improve cognitive performance for social stimuli.

Received 5 March 2007; Reviewed 25 April 2007; Revised 28 June 2007; Accepted 15 July 2007; First published online 13 August 2007

Key words: Depression, escitalopram, facial identity, memory.

Introduction
Mood disorders are associated with cognitive abnormalities, especially in the perception and consolidation of emotional stimuli (Leppänen, 2006). In addition, depressed individuals exhibit impaired social functioning (Cooley and Nowicki, 1989) mainly due to the accompanying cognitive deficits, which handicap interpersonal processes (Hale, 1998; Pine et al., 2004). According to the dominant cognitive paradigm for depression, Beck’s model, maladaptive cognition is implicated in both the aetiology and maintenance of the depressive process (Beck et al., 1979). Depressed individuals have the tendency to appraise themselves, others and their daily events with negative expectancies (Beck et al., 1979; Lewinsohn et al., 1981), and to selectively recall negative information or exhibit an attentional bias towards negative emotional cues, a finding known as abnormal or negative emotional memory bias of depression (Bradley et al., 1995; Gotlib et al., 2004; Leppänen, 2006; Surguladze et al., 2004; Zakzanis et al., 1998). Additionally, depressive patients tend to attribute negative events (Sweeney et al., 1986) and negative self-evaluations to themselves (Giesler et al., 1996). Depressive individuals specifically endorse and recall...
less positive information and organize positive self-relevant information with less interconnectedness than anxious individuals and controls, suggesting that they have an interconnected negative self-representational system and lack a well-organized positive template of self (Dozois and Dobson, 2001).

Thus, dysfunctional interpersonal interactions, as a consequence of negative bias, may sustain depression symptoms (Coyne et al., 1991). Depressive persons elicit support behaviour, intermixed with rejection attitudes, from persons in their general surroundings, and continuously increase their support-seeking behaviour until these persons eventually withdraw. Interpersonal interactions of depressive persons, such as giving or receiving social support, are heavily impaired (McNaughton et al., 1992), and their readiness to perceive and attend to negative aspects in interpersonal relationships may lead to decreased social support (Gotlib and Hammen, 1992). Finally, this maladaptive process contributes decisively to increased risk of depression chronicity (Brown et al., 1994). In addition, abnormalities in the processing of emotional information heighten the risk of the development of mood disorders (Leppänen, 2006). Therefore, understanding the negative aspects of the cognitive processes that lead to maladaptive interpersonal interactions in depression and improvement of these cognitive difficulties may help patients.

Facial expressions are stimuli with a high arousal effect and the recognition of emotional facial expressions is a perceptual-interpretive process that is highly developed in human and non-human primates, reflecting its social and behavioural importance (Rubinow and Post, 1992). Facial expressions of basic emotions are archetypal social cues that are instantly recognizable and modulate interpersonal behaviour (McArthur and Baron, 1983). Cross-cultural studies indicate that the recognition and expression of basic emotions in facial expressions show universal similarity (Ekman, 1993). Therefore, facial expressions are useful tools to employ in the study of cognitive processes in interpersonal interactions.

In the present study, using an emotional facial recognition test, which applies the signal detection and discrimination paradigm, we investigated the memory for facial identity in elderly depressive patients before and after the treatment with a selective serotonin reuptake inhibitor (SSRI), escitalopram. Since depression is a common disorder in the elderly greatly disabling them in their individual and social behaviour, we hypothesize that antidepressive treatment with escitalopram may improve the cognitive parameters contributing to the recovery process. The main hypotheses of this investigation were: (1) Depressive patients have impaired identity recognition memory compared to healthy age-matched control subjects. (2) Elderly control subjects show the well-documented emotional expression bias that they better recognize happy identities. (3) Depressive patients do not show this bias. (4) Treatment of depressive patients with escitalopram improves affective and global cognitive scores. (5) Treatment of depressive patients with escitalopram restores identity recognition memory deficits. (6) Improvement of depression correlates with improvement of memory.

Method

Study design

The present study was a 4-wk, single-centre, open-label trial to assess the effects of treatment with escitalopram on affective and cognitive symptoms, and on memory for facial identity in elderly depressed patients compared to healthy age-matched controls. The protocol was approved by the local Ethics Committee and conformed to the provisions of the Declaration of Helsinki. Written informed consent was obtained, and full and adequate oral and written information about the objectives of the study, possible therapeutical advantages and side-effects were given to the participants.

The inclusion criteria were a confirmed diagnosis of a current depressive episode according to ICD-10 criteria (major depression, first episode), permanent medical or social care available during the study, written informed consent and age >65 years. The exclusion criteria included known sensitivity to escitalopram, evidence of severe and/or chronic renal, hepatic, cardiovascular, pulmonary or gastrointestinal impairment or cancer, other psychiatric disorders or dementia, drug abuse, concomitant medication with clonidine or beta-blockers, and participation in any other drug trial. Subjects were free to withdraw their informed consent at any time, without prejudice to further treatment.

Patient data was collected during three visits. Visit 1: during the run-in period for baseline assessments to check inclusion and exclusion criteria; visit 2, 1 d prior to commencing study drug, and visit 3 at the end of the fourth week of treatment. The facial picture recognition test and the additional psychometric test battery were performed twice during visits 2 and 3 in depressed patients. Since all patients with depression were in-patients, they all underwent a routine physical and laboratory examination.
and electrocardiogram during the baseline period. Healthy elderly controls were assessed only during visits 1 and 2, and the facial picture recognition test and the additional psychometric tests were performed once during visit 2.

**Patients and control subjects**

All patients with depression were in-patients hospitalized on the gerontopsychiatric ward. Twenty-two patients were included in the study. Four patients dropped out during the course of the study because of withdrawal of informed consent, evidence of psychotic symptoms or acute infection. Thus, a total of 18 patients finished the 4-wk treatment period and could be evaluated: 14 women and 4 men (Table 1), mean age (± S.E.M.) 76.2 ± 1.8 yr. Additionally, 22 elderly controls, 16 women and 6 men, were included in the study (mean age 76.9 ± 1.8 yr), who were recruited by local advertisement and from retirement homes. Only healthy elderly participants were included in the study without acute or chronic severe diseases which was confirmed by physical examination and a report from their medical caregivers.

**Medication**

Concomitant medication was allowed with the exception of clonidine and beta-blockers. Concomitant psychiatric medication, especially benzodiazepines and hypnotics, were only allowed during the initial acute phase of the depression starting after visit 2 assessments. Then concomitant psychiatric medication was withdrawn during the next 2 wk of treatment. Escitalopram was chosen as the antidepressive medication since the R-enantiomer present in citalopram has been suggested to reduce the efficacy of S-enantiomer (escitalopram) which is mainly responsible for the serotonin reuptake inhibitory activity of the compound (Sánchez et al., 2004). The starting dose was 5 mg, which was increased in 5-mg steps every 1–2 wk, based on the clinical judgement of the investigators. The maximum allowed dose of escitalopram was 20 mg.

**Experimental stimuli and facial picture recognition test**

For testing the memory for facial identity picture photographs of male faces with happy (positive) or angry (negative) expressions were presented on a computer screen approximately 60 cm in front of the seated participants. The two emotional expressions ‘happy’ and ‘angry’ were chosen because of their high social relevance in approach and avoidance dimensions. The generation of test material is described in detail in a previous study (Savaskan et al., 2007).

Participants were asked to look carefully at the presented faces, and especially observe their characteristics and emotional expressions, in order to recognize them later in the second part of the test. For the encoding task, participants saw 30 randomly assorted faces with angry or happy expressions of 30 different subjects. Each picture was presented for 10 s, and there was a 3-s interval between each picture, appearing as a white screen. After a 10-min retention interval, 60 faces were presented to the participants in the recognition task, all with neutral expression. Thirty pictures included in the recognition task were the neutral faces of 30 individuals presented during the encoding task and the remaining 30 pictures showed new faces. After each picture participants were asked to identify each face as old or new.

Then the sensitivity index d’ from signal detection theory was calculated to get a bias-free measure of memory strength for identity recognition (Wickens, 2002). For identity recognition an overall hit and false-alarm rate and two expression-specific hit rates were calculated for each subject. These values were used to calculate d’ as $z(\text{hit rate}) - z(\text{false alarm rate})$ for the overall and the two expression-specific recognition performances for each subject. To compare memory performances between and within the different groups several ANOVAs were conducted with d’ as the dependent variable. As escitalopram was expected to improve cognitive function and memory, hypothesis 5 was tested with a-priori constructed, one-sided contrast based on $t$ tests. A $\chi^2$ test was used to explore the memory bias for faces acquired with happy expression. Effects of subject education were assessed by Student’s $t$ test and Mann–Whitney U test again with $d’$ as the dependent variable.

**Psychometric test battery**

**Geriatric Depression Scale (GDS)**

The GDS was originally devised by gathering 100 questions relating to depression in older people, and then selecting the 30 that correlated best with the total score, and has shown high sensitivity and specificity (Yesavage et al., 1983). Each question has a yes/no answer, with the scoring dependent on the answer given. Scores >6 indicate a depressive disorder, and only subjects with scores >6 were included as depressive patients in the study. The mean GDS baseline scores of the participants was $9.4 ± 0.4$ for elderly depressed patients and $1.2 ± 0.3$ for age-matched controls (Table 1).
The MMSE is probably the most widely used assessment scale for cognitive functioning and was originally created to differentiate organic from functional organic disorders (Folstein et al., 1995). The MMSE has a maximum score of 30 points, with different domains assessed: orientation to time and

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Education: (1) primary, (2) secondary, (3) tertiary; MMSE-1, Mini-Mental-State-Examination baseline; MMSE-2, after 4 wk of treatment with SSRI; GDS-1, Geriatric Depression Scale baseline; GDS-2, after 4 wk of treatment with SSRI; SSRI, maximum dose (mg) of escitalopram.
place, registration of three words, attention and calculation, recall of three words, language and visual construction. Scores <26 indicate cognitive disturbances and need further evaluation to exclude organic or non-organic cognitive disorders. The MMSE was performed twice in depressed patients at baseline and after 4-wk treatment period to assess cognitive improvement. Since all patients were in-patients, those patients with a MMSE score <26 underwent a routine dementia screening procedure including neuroimaging and a Consortium to Establish a Registry for Alzheimer’s Disease (CERAD) test battery to exclude dementia. The mean MMSE baseline scores of the participants were 26.9 ± 0.5 for elderly depressed patients and 29 ± 0.2 for age-matched controls (Table 1).

Results

Demographic data and the results of GDS and MMSE assessments are summarized in Table 1. Eighteen elderly depressed patients (excluding four drop-outs) and 22 age-matched controls were evaluated. No severe adverse events were observed during the therapy with escitalopram in depressed patients. Three patients complained of mild adverse events such as gastrointestinal discomfort and nausea in the first week of the antidepressive therapy. Two patients had urinary infections during the treatment period and were treated with norfloxacin for 5 d. However, none of these two patients had antibiotic therapy during the visit 3 assessments. The mean dose of escitalopram at the end of the 4-wk treatment period was 16.1 ± 0.8 mg.

ANOVA was performed with the between-subject factor ‘group’ and the within-subject factor ‘emotional expression’ – the latter based on d’ values calculated separately for acquired faces with happy and angry expression – and revealed that depressive patients have lower identity recognition memory performance than healthy age-matched control subjects (hypothesis 1) (F1,26 = 4.6, p = 0.038; see also Figure 1). When examining this difference in more detail it appeared that this difference was mainly due to memory performance of identities acquired with happy facial expressions (p = 0.018, see Figure 1).

Subjects in the control group had a better recognition of identities with a happy facial expression (hypothesis 2) (p = 0.046, see Figure 1). This, however, was not the case for depressed patients, neither before, nor after treatment with escitalopram (hypothesis 3). There were seven out of 22 control subjects who had a better identity recognition for faces acquired with angry expression and 15 who had a better or equal identity recognition for faces acquired with happy expression. However, 11 out of 18 depressed patients showed better identity recognition for faces acquired with angry expression and seven did not show this behaviour. An a-priori constructed one-sided χ² test was based on this distribution and revealed statistical significance (p = 0.03). Thus, with respect to the well-established identity recognition memory bias, depressed patients failed to respond to happy-face stimuli.

Within the treatment group GDS scores improved significantly from baseline (p < 0.0001) after the 4-wk treatment period (hypothesis 4). Group mean scores were 9.4 (±0.4) before and 4.7 (±0.6) after treatment. MMSE values also improved significantly (p = 0.023) after treatment from 26.8 (±0.5) to 27.9 (±0.4).

Treatment of depressive patients with escitalopram did not improve identity recognition memory for faces acquired with happy expression. However, escitalopram improved identity recognition memory for faces acquired with angry expression. Before treatment the mean d’ was 0.46 (±0.13), and after treatment it was 0.62 (0.1, p = 0.05) (hypothesis 5). Individual improvement (change in GDS or MMSE scores) after treatment with escitalopram did not significantly correlate with changes in identity recognition performance (hypothesis 6).

Discussion

The present study shows significant effects of antidepressive therapy on affective and cognitive
parameters in elderly depressed patients as shown by
GDS and MMSE results. In addition, antidepressive
therapy was able to improve memory for facial identity
for negative stimuli. The main findings at baseline
were a general reduction in memory performance in
elderly depressed patients and a bias towards positive
(happy) facial identities in healthy elderly controls.
The latter is in accordance with our previous findings
in healthy elderly subjects (Savaskan et al., 2007).
Happy faces were found to be better recognized in all
observed age groups (young adults: 20–40 yr; elderly
adults: 60–80 yr; and very old adults: > 80 yr) than
angry faces (Savaskan et al., 2007). Although there was
a continuous overall decrease in recognition of both
happy and angry faces with advanced age in those
healthy individuals, the effect favouring happy facial
expressions was found to be stable in old and very old
adults. Decreased facial identity recognition was sug-
Aged to underlie difficulties in emotion processing in
the elderly, and to contribute to behavioural and social
difficulties in their daily life.

Although there was a positive bias towards happy
facial identities in age-matched control subjects, this
was not observed in patients with depression prior to
and after the treatment period in the present study.
Thus, 61.1% of patients with depression showed a
better identity recognition for faces with angry ex-
pression, whereas only 31.8% of control subjects
showed this behaviour. This is in accordance with
previous studies suggesting a negative cognitive bias
in depressed patients: a review summarizing the re-
results of studies investigating emotional information
processing in mood disorders has shown this negative
bias for young depressed patients (Leppänen, 2006).
In addition, young depressed patients were shown to
have a general impairment in displaying emotional
facial expressions (Wexler et al., 1994), and were
generally impaired in the recognition of affect in the
facial expressions (Rubinow and Post, 1992). Their
interpersonal difficulties have been suggested to be
strongly linked to the fact that they exhibit difficulty in
accurately decoding facial expressions of emotions as
well as in their behavioural and emotional responses
to these expressions (Persad and Polivy, 1993). Young
depressed patients, relative to the non-depressed
controls, were found to make more errors in rec-
ognizing facial expressions and reported more
tensing, higher fear and depression reactions, and
feeling less comfortable with their own emotional re-
actions.
In general, emotion perception is disproportionately
negatively affected relative to other cognitive functions
in depressed patients (Langenecker et al., 2005), and
depressed patients show subtle impairments in
discrimination accuracy and predominant bias away
from the identification of happy expressions
(Surguladze et al., 2004). On the other hand, clinically
stabilized depressed in-patients were significantly
slower in responding to positive faces than normal
subjects, whereas they did not show performance
differences in the detection of negative faces, suggest-
ing that depressive mood may also be associated with
a reduced spatial attention to positive facial expression
(Suslow et al., 2001). Moreover, some of these abnor-
malities in the processing of emotional information
persisted after symptom remission (Leppänen, 2006).
This may explain why patients failed to improve
their recognition of happy facial expressions after the
treatment period in the present study. Another factor
may be that depressive patients require significantly
greater intensity of emotion than control subjects to
correctly identify happy expressions (Joormann and
Gotlib, 2006). Interestingly, poorer memory perform-
ance for emotional facial expressions was significantly
associated with larger left amygdala volumes in de-
pressed patients taking antidepressant medication
(Weniger et al., 2006).

One limitation of the present study may be the
dominance of female subjects in both groups which
represents the demographics of the main population
in this age group. In a previous study gender effects
were reported on memory for facial identity: women
were found to identify more male faces correctly than
female faces, irrespective of the emotion expressed
(Rahman et al., 2004). Since only pictures of male faces
were included in the present study, this effect may not
limit study results. Two other studies demonstrated a
female advantage across emotions regardless of the
sex of the face presented (Campbell et al., 2002; Thayer
and Jonsen, 2000) whilst one reported that the sex of
the subject interacted with the sex of the face (Erwin
et al., 1992). Women were found to be more sensitive
to happiness in male faces (Erwin et al., 1992) whereas
later data have shown women to be more accurate at
identifying male faces regardless of emotion (Rahman
et al., 2004). Nevertheless, our previous data have
shown that gender-related differences in facial identity
may not have a significant impact in the elderly
(Savaskan et al., 2007).

There was a significant improvement from baseline
in GDS and MMSE scores during the 4-wk treatment
period in the present study, and escitalopram was well
tolerated. Mild adverse events such as gastrointestinal
discomfort and nausea were observed in three of the 22
patients within the first week of treatment. The effects
of citalopram on cognitive processing of emotional
cues have been studied previously in healthy young volunteers (Harmer et al., 2003, 2004). Volunteers receiving a single dose of citalopram were found to detect a higher number of facial expressions of fear and happiness, with reduced response times, relative to those given a placebo (Harmer et al., 2003). Citalopram also reduced the identification of the negative facial expressions of anger and fear after 7 d treatment, and abolished the increased startle response found in the context of negative affective images (Harmer et al., 2004). In addition, it increased the relative recall of positive (vs. negative) emotional material. Thus, volunteers receiving citalopram for 7 d showed decreased amygdala responses to masked presentations of threat compared to placebo, and citalopram was able to reduce responses within the hippocampus and medial prefrontal cortex specifically during the fear-relevant stimuli (Harmer et al., 2006). Interestingly, there was no effect of citalopram on the neural or behavioural response to happy facial expressions in the latter study. These results suggest a direct effect of serotonin potentiation on amygdala response to threat-relevant stimuli in humans. Since elderly depressed patients were investigated, not only age, but also the differential effects of escitalopram therapy on emotional processing of negative or positive stimuli may account for the failure of these patients to show a positive bias after the treatment period in the present study. It has been suggested that antidepressant therapy may not directly affect mood but may initiate a cascade of changes in emotional processing, which ultimately affects low mood and anxiety through changes in social reinforcement and the detection of environmental threat (Harmer et al., 2006). Elderly subjects have an overall reduction in cognitive performance for identity memory (Savaskan et al., 2006), and therefore, elderly patients might need a longer treatment period to overcome the memory deficits for emotional stimuli. However, the positive effect of the SSRI on cognitive processing of negative stimuli may provide an additional clue in the treatment of depression.

In conclusion, the present data show that elderly depressed patients have not only affective and overall cognitive symptoms, but also deficits in facial identity recognition memory, especially for identities with happy facial expressions. This may provide a critical performance deficit complicating interpersonal behaviour difficulties in depressed patients. Antidepressant therapy with escitalopram improved mood, overall cognitive performance and the memory for negative facial stimuli, but not for positive stimuli. The SSRI treatment seems to be effective in decreasing the negative bias of depression and may help improve patients’ maladaptive social interactions.

Acknowledgements
S. Müller and the study equipment were supported by an unrestricted grant from Lundbeck (Switzerland), who had no responsibility for the study protocol, data analysis, data interpretation, or writing of the manuscript.

Statement of Interest
None.

References


