



Social support and striatal dopaminergic activities: Is there a connection?

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ABSTRACT

Objectives: Although patients' social support is a critical factor for the prognosis of mental disorder treatments, biological mechanisms responsible for the impact of social support remain scarcely explored. We speculated that there may be an association between social support and central dopaminergic activities in humans.

Methods: A total of 65 medicated patients with schizophrenia and their primary first-degree caregivers and 54 healthy volunteers were recruited for Studies 1 and 2, respectively. In Study 1, the extrapyramidal side effects (EPS) of medicated patients with schizophrenia and the social support scores of their caregivers were examined. In Study 2, the availability of striatal D₂/D₃ receptors, dopamine transporters (DAT) and social support scores were measured in 54 healthy volunteers.

Result: Study 1: the EPS scores of medicated patients with schizophrenia were negatively correlated with the social support scores of their relatives. Study 2: a positive correlation between the subjective social support scores and striatal DAT availability was noted.

Conclusion: The central dopaminergic activity may be linked to the sense of social support.

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1. Introduction for Study 1

In humans, social support could be as critical as maternal behaviors in the maintenance of health and survival. Social support is one of the important domains of social behavior, which not only benefits mental health and physical well-being, but also buffers the effects of stress (Kawachi and Berkman, 2001; Lee et al., 2006; Norbeck, 1988; Reblin and Uchino, 2008). Several groups of researchers have demonstrated that adequate social support may protect people in crisis against depression (Brown et al., 1975; Bruce, 2002; Oxman et al., 1992). Likewise, the availability of social support has been repeatedly

demonstrated as an important variable in leading patients with mental problems to better adjust to new demands (Berkman et al., 2000; Lee et al., 2006; Norbeck, 1988).

Although the importance of social support in the pathogenesis and treatment of mental disorders has been noted, social support is traditionally treated as an outside-skin behavioral factor, rather than a within-skin physiological factor. Nevertheless, the dichotomy between gene/biological factor and the environment may be too arbitrary. Recent studies have begun to elucidate the roles played in social cognition by special neural structures, particularly in the cortical region and the amygdale (Adolphs, 2006). However, the molecular underpinning of social cognition remains an underexplored domain. Several neurotransmitters appear to play important roles in social behaviors (Brunner et al., 1993; Capitanio et al., 2008; Davidson et al., 2000; Ferguson et al., 2000; Insel et al., 1999; Knutson et al., 1998; Panksepp, 1998; Raleigh et al., 1996; Tsai et al., 2009a; Yang et al., 2007; Young et al., 1998). The relationship between social support measures and its biological substrates, particularly the central neurochemical systems, has not yet been well elucidated. Social support measures and the serotonin transporter gene have both been reported to modulate the incidence and severity of depression in maltreated children (Kaufman et al., 2004), while central dopaminergic functions seemed to play a role in the affiliation and social attachment traits (Depue and Morrone-Strupinsky, 2005).

Abbreviations: DAT, dopamine transporter; EPS, extrapyramidal side effect; FWHM, full-width at half-maximum; IBZM, iodobenzamide; MRI, magnetic resonance imaging; Oc, occipital cortex; PCS, perceived crisis support score; PRS, perceived routine support score; RCS, received crisis support score; ROI, region of interest; RRS, received routine support score; SPECT, single positron emission computed tomography; St, striatum; TRODAT-1, [2-[[[2-[[[3-(4-chlorophenyl)-8-methyl-8-azabicyclo [3.2.1] oct-2-yl]methyl] (2-mercaptoethyl) amino] ethyl] amino]ethanethiolato (3-)-N₂N_{2'}S₂S_{2'}]oxo-[1R-(exo-exo)].

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Early disruption of the central dopaminergic system in animals has been shown to affect brain maturation (Lauder, 1988). Normal development and maturation of the central dopaminergic system is responsible for the motor function, execution emotion, perception and expression. Ontogenetically, successful dopaminergic innervation may further assure the normal operation of cognitive functions in mammals (Previc, 1999). Post-weaning social isolation may render a range of neurobehavioral changes in adult rats. Such changes have been revealed to be associated with the altered dopaminergic functions (Lapiz et al., 2003). A direct relationship between central dopaminergic imbalance and impaired maternal behaviors and social activities for the survival of the species has been reported in rats (Li et al., 2005; Li et al., 2004). Silk et al. (2003) also reported that the sociality of adult female baboons correlated positively with the infant survival rate, suggesting the adaptive value of sociality.

The development of central dopaminergic innervations may be associated with the ability of organisms to adapt to both internal and external constraints, either during the course of evolution or development. In addition, the poor interpersonal relationships and social skills in patients with schizophrenia have been linked to information processing abnormalities in the brain, in which dopamine dysfunction has been also suggested (Brunet-Gouet and Decety, 2006; Tarbox and Pogue-Geile, 2008). Using the sample of the National Longitudinal Study of Adolescent Health, Guo and Tillman (2009) also demonstrated that social support measures may be partially determined by the polymorphism of DRD2 and DRD4. As mentioned above, there may be an association between social support measures and central dopaminergic activities in humans.

To achieve a better understanding of the relationship between social support measures and central dopaminergic functions in humans, we present two studies in this paper. This first one (Study 1) is an observation study in which the relationship between the severity of extrapyramidal side effects (EPS) in medicated patients with schizophrenia and the social support of the primary caregivers of the patients (first-degree family members) was examined. Recently, genetic factors have been suggested to play a role in the susceptibility to EPS (Basile et al., 2002; Segman et al., 2002). Honer et al. (2005) showed that many first-episode patients with no exposure to antipsychotics also had EPS, particularly in patients with a family history of movement disorders. Lencer et al. (2004) also demonstrated that family history of primary movement disorder is the most important predictor for neuroleptic-induced EPS in patients. Since central dopaminergic activities play an important role in EPS, these findings suggested possible shared genetic factors in EPS as well as in central dopaminergic activities.

It is known that antipsychotics may induce EPS. If the relationship between social support and central dopaminergic activities does exist, we expect that there will be a negative association between the severity of EPS in patients with schizophrenia and the social support measures of their primary caregivers after controlling the dosage of antipsychotics.

Based on the above-mentioned findings of previous studies, we hypothesized that there may be an indirect connection between social support measures and EPS scores in Study 1.

1.1. Materials and methods

1.1.1. Methods for Study 1

1.1.1.1. Subjects. Stable patients with schizophrenia who met the criteria of DMS-IV and who had been taking antipsychotics for more than one year were consecutively enrolled at the psychiatric outpatient clinic of three hospitals. The original cohort for Study 1 is for pharmacoeconomic evaluation in which 72 patients and their caregivers were recruited. In Study 1, only the first-degree relatives serving as these patients' major caregivers from Lee et al.'s (2008) study were recruited. Of the 65 patients, 37 were males and 28 were females. Demographic data of these patients included age (33.03 ± 8.71 years old), duration of

illness (10.63 ± 7.87 years), years of education (10.63 ± 2.36 years), frequency of hospitalization (1.53 ± 1.46), antipsychotic dosage with chlorpromazine equivalence (375 ± 191 mg), and the total scores of the Positive and Negative Syndrome Scale (PANSS) (68.31 ± 17.12). The major caregiver was defined according to the following criteria: 1. living with the patient; 2. entitled to decide the treatment mode and medication type; and 3. responsible for the daily care of the patient. Informed consent was obtained from patients and their caregivers. The Ethics Committee for Humans Research at National Cheng Kung University Hospital approved the Study 1 protocol.

1.1.1.2. Measurement. The Extrapyramidal Symptom Rating Scale (ESRS) (Chouinard et al., 1980) was used to evaluate the severity of the EPS score of the patients with schizophrenia. The self-reported Measure of Support Function (MSF) (Lin et al., 1999) questionnaire was administered to the patients' caregivers. The MSF is composed of two dimensions of social support: 1. one dimension for perceived versus received social support; and 2. another dimension for the social support received under routine versus crisis status. The perceived support referred to the perceived availability of support when needed, and the appraisal of the adequacy and the quality of such support, e.g. "Could you get someone to lend you a car for an emergency situation if you needed it?" The received support referred to the nature and frequency of specific support transactions actually received in a real situation. In this study, perceived and received support represented the subjective and objective social support, respectively. The support under routine status depicted either the support received or perceived with the daily activities (e.g. child care and grocery shopping). The support in a crisis status revealed the perceived or received support in an exigency (e.g., a car accident). Thus, this two-dimensional questionnaire constituted four subscales, the perceived crisis support (PCS), the perceived routine support (PRS), the received crisis support (RCS), and the received routine support (RRS). The Cronbach's α , which is an index for internal consistency, of all of the subscales of the MSF were all greater than 0.93. The higher MSF scores indicate more social support. In this study, only the PRS and the PCS scores were used since the perceived domain of social support is likely to have direct effects on mental health (Lee et al., 2006). Spearman's ρ correlation test was conducted to examine the correlation between PANSS, social support measures and EPS score, all of which are ordinal variables. In addition, partial correlation was used to assess the relationship between social support scores and the EPS scores while controlling for the dosage of the medication.

1.2. Results for Study 1

The mean scores of PCS and PRS of the major caregivers and the mean score of the EPS score of the patients were 24.31 ± 5.84 , 21.20 ± 8.04 , and 2.42 ± 1.34 , respectively. The correlation matrix of the relationships among the PANSS scores, EPS scores, social support measures, age, and dosage of chlorpromazine equivalence is presented in Table 1. The PANSS scores correlated with the EPS scores while the dosage of chlorpromazine equivalence correlated with the EPS and social support measures. After partialling out the effect of dosage of chlorpromazine equivalence, a marginally significant correlation between EPS scores and PCS scores was found ($r = -0.25$, $p = 0.05$) (Fig. 1). However, there was no evident association between the PRS scores and the EPS scores ($r = -0.48$; $p = 0.68$).

1.3. Discussion for Study 1

Our results showed that high EPS scores in patients with schizophrenia were associated with low social support scores in their first-degree caregivers. Traditionally, the availability of social support is treated as an environmental factor in the pathogenesis of mental disorders (Kaufman et al., 2004; Kendler, 2001). Therefore, it is not surprising to find such negative association between the PCS and EPS

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