Situation Awareness in Obsessive Compulsive Disorder and Their Relatives: an Endophenotype Study

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ABSTRACT

Introduction: It has been theorized that endophenotype models will help to understand the etiology of heterogeneous brain disorders such as obsessive-compulsive disorder (OCD). In this study, it was aimed to determine whether “situational awareness” impairments which can be defined as partially naturalistic working memory deficits, are an endophenotype for OCD.

Methods: In this study, situational awareness (SA) task performances of 67 OCD patients, 50 their unaffected first-degree relatives, and 41 healthy controls who matched with regard to sex, age and years of education were measured to investigate endophenotypes in OCD. For this purpose, a visuospatial working memory test was used.

Results: As a result, the relatives showed a task performance between

patients with OCD and control group in both SA1 and SA2 tasks. Patients with OCD performed significantly worse than control group on SA1 single and dual task. On the other hand, there were no significant differences between relatives and patients of any SA assessment.

Conclusion: These results indicated that poor situational awareness may be a candidate endophenotype for OCD. Early perceptual dysfunctions such as poor performance on SA1 task can mediate the genetic risk for OCD.

Keywords: Obsessive-compulsive disorder, situation awareness, endophenotype, working memory, visuo-spatial working memory, neuropsychology

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INTRODUCTION

Obsessive-compulsive disorder (OCD) is characterized by repetitive ritualized behaviors as well as recurrent, resistant, and unwanted thoughts; as a result, patients with OCD often experience a significant loss of function (1,2). Since previous studies on behavioral and clinical phenotypes have not been able to identify the genes involved in the pathogenesis of OCD, more recent studies have focused on objective and measurable parameters, including endophenotypes (3). It has been suggested that these parameters may be able to more accurately identify the causal chain between genes and clinical manifestations (4), and may be valuable in identifying those at risk of disease development, clarifying the etiological factors, and developing new treatment protocols (5). In this context, some have suggested that neurocognitive impairments in both OCD patients and their first-degree relatives may be appropriate endophenotypic markers that may aid in the elucidation of the genetic mechanisms of OCD (6).

Literature reveals that visual-spatial integration and working memory functions are the cognitive abilities most commonly observed as disorders in OCD patients. However, to our knowledge, there are few studies measuring these functions in OCD patients' first-degree relatives (7,8). Until recently, measurement of the visual-spatial integration and working

memory functions of OCD patients and their first-degree relatives has been done with conventional tests requiring a static and limited workload that are often semantically meaningless. However, if these visual-spatial integration/working memory functions are associated with obsessions and compulsions that occur during daily life (which is a requirement of being an endophenotype), then neuropsychological tests with high ecological value may be more useful in this field than conventional tests. Since tested visual information is changing constantly over time, has semantic meaning, and requires more workload, these tests will be more ecological. (9). In reality, conventional tests do not focus on measuring this “naturalistic awareness” situation in everyday life, but rather, they focus on cognitive abilities that are partially categorized as artificial, such as attention, memory, response inhibition, and set shifting. However, it is believed that in daily life, these cognitive abilities work together, not separately, and that the brain areas that are thought to be responsible for these capabilities function as a network (10). The situational awareness test is used to measure the perception and interpretation of visual information in everyday life, rather than focusing on specific cognitive abilities; in the literature, this test has long been used to measure the level of awareness in occupational groups such as aircraft pilots, machine operators, and doctors (11).

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Situational awareness is defined as a person's ability to perceive and understand a situation that is occurring around him/herself. Situational awareness tests utilize three stages of evaluation. The first stage measures the instantaneous perception of elements moving in space over time, the second stage measures the integration and comprehension of the features of these elements (such as space and shape), and the third stage measures the prediction of the future states of these elements. Cognitive functions such as attention, memory, and working memory are known to be affected by one's situational awareness. The situational awareness paradigm is used to examine how these cognitive functions are used in conjunction in order to understand one's environment and to make appropriate decisions (12); therefore, the situational awareness paradigm adds validity to conventional cognitive tests (13). An example of the first stage of situational awareness is a situation where, upon leaving his/her house, a person perceives that one of his/her stove buttons is in a different position from the others. An example of the second stage is one's comprehension that the stove was left on. His/her deduction that it will be dangerous to leave the stove on until he/she returns home is an example of the third stage. A person with good situational awareness is expected to make the decision to turn off the stove without dilemma. Impaired situational awareness is thought to be associated with impaired decision-making function, which is believed to be the primary mechanism for the development of the symptoms of OCD (12,14). Although situational awareness tests share some similarities with the visual working memory tests previously used in OCD patients (15,16), they differ in that they make evaluations in three different stages, and can measure function at a higher capacity, particularly in the second and third stages. Since working memory tests requiring a high capacity may have higher sensitivity in OCD patients (15), the use of these tests in OCD patients may facilitate the detection of cognitive disorders.

One study examining the "situational awareness" of OCD patients found that there were disorders in the early stages of visual perception and comprehension by binding visual stimuli mediated by attention. In addition, that study also emphasized that particularly early cognitive function disorders were correlated with some obsessive-compulsive symptoms (17). These findings suggest that situational awareness tests may be used for identifying the cognitive basis of OCD. As our current study is the first to use these tests on the first-degree relatives of OCD patients, our study may provide useful information about whether the disorders in OCD patients are endophenotypes.

In consideration of previously published data, the current study aimed to compare situational awareness, which is thought to be an endophenotypic marker in OCD, among OCD patients, their first-degree relatives, and a control group. Our study tested the hypothesis that situational awareness disorder is a cognitive endophenotype for OCD. If the first-degree relatives of OCD patients perform worse than the controls or similar to the OCD patients, then we can confirm that situational awareness is an endophenotype for OCD.

METHODS

Participants

A total of 67 patients who presented to the Pamukkale University Medical Faculty Psychiatric Hospital Polyclinics and agreed to participate were included in the study. All of the 67 included patients were between the ages of 18 and 65 years and were diagnosed with OCD according to DSM-IV diagnostic criteria. This study also included 50 healthy first-degree relatives of these patients and 41 healthy controls that were randomly selected, had no personal or family history of psychiatric disease, and were matched with the other groups in terms of age, gender, and education level. The following were excluded from the current study: (I) those who did not read and sign the informed consent form,

(II) illiterate individuals, (III) patients with psychotic disorder, bipolar disorder, mental retardation, alcohol-drug use disorder, or organic mental disorder (e.g., dementia, delirium, and head trauma), those who received electroconvulsive therapy or transcranial magnetic stimulation (TMS) in the last 6 months, or those with significant accompanying medical or neurological disease, and (IV) patients with Hamilton Depression Rating Scale (HAM-D) scores of 17 and above. Based on the exclusion criteria, we excluded 3 patients with depressive disorder, 7 patients with psychosis, 9 patients with comorbidity of bipolar disorder, 1 patient with Multiple Sclerosis, 3 patients who had received TMS treatment in the last 6 months, and 2 illiterate patients. This study was approved by the Pamukkale University Ethical Committee for Non-Interventional Clinical Investigations (decision no. 57285 on 30.09.2014).

Procedure

Recorded from each patient using an interview form prepared by the researches were age, gender, marital status, duration of education, age at onset of disease, duration of disease, comorbidities, and current medications. All participants underwent a structured clinical interview (SCID-I) by an experienced psychiatrist according to DSM-IV-TR diagnostic criteria.

The Yale-Brown Obsessive Compulsive Scale (Y-BOCS) was used to assess the severity of current symptoms, while the Maudsley Obsessive Compulsive Inventory (MOCI) was used to determine the prevalence of obsessive-compulsive symptoms in the patients, their relatives, and the controls. In addition, all of the patients were evaluated with the Hamilton Depression Rating Scale (HAM-D) and the Hamilton Anxiety Rating Scale (HAM-A) in order to determine the severity of each patient's depression and anxiety. After completing the clinical interviews and scales, participants were taken to a quiet room in which they underwent computerized neurocognitive tests (HP Pro One 400 personal computer with a 15.4 inch touch screen and 1440×900 pixel screen resolution). All of the tests were performed with the participant at a distance of 25 cm from the screen under the supervision of the researcher. The Situational awareness Test (SA test) in the Psychology Experiment Building Language (PEBL) Test Battery (version 0.13) was used to assess situational awareness (18). This test was modified in accordance with the requirements and translated into Turkish.

Scales

DSM IV Structured Clinical Interview (SCID-I): The DSM IV Structured Clinical Interview (SCID-I) is a structured clinical interview scale developed for the analysis of Axis I disorders (19). The clinician uses the scale to rank signs seen throughout the patient's life and within the last month using a categorical system, and these data are placed in an algorithm in order to obtain an Axis I diagnosis. The Turkish adaptation and reliability studies on SCID-I were carried out by Özkürkçügil et al. in 1999 (20).

Yale Brown Obsessive Compulsive Disorder Scale (Y-BOCS): The Yale Brown Obsessive Compulsive Disorder Scale (YBOCS) was developed by Goodman et al. to assess the severity of obsessive-compulsive symptoms, clinical course, and treatment outcomes (21). The severities of the obsessions and compulsions are graded on a 0 to 4 scale considering each of the following points: How much time does each symptom take for a patient? How does it affect the patient's normal life? How much does it disturb the patient? How much can the patient resist and control? The Turkish validity and reliability study of the scale was performed by Karamustafaloğlu et al. and Tek et al. (22, 23).

Maudsley Obsessive Compulsive Inventory (MOCI): The Maudsley Obsessive Compulsive Inventory (MOCI) is a self-assessment scale used to assess the type and prevalence of obsessive-compulsive symptoms in

OCD patients and healthy individuals. The original scale was developed by Hodgson and Rachman in 1977 (24). There are four subscales (i.e., cleaning, checking, doubting, and slowness) that are coded as true or false. A 7-item rumination subscale from the Minnesota Multiphasic Personality Inventory (MMPI) was added to the Turkish adaptation form. The Turkish version of the scale was determined to have sufficient validity and reliability values (25).

Hamilton Depression Rating Scale (HAM-D): The Hamilton Depression Rating Scale (HAM-D) was developed by Max Hamilton in 1960 and is widely used to measure the severity of depression and to identify the clinical symptom patterns in past week (26). It is a 4 point Likert scale. The validity and reliability of the Turkish version of the scale were studied by Akdemir et al. in 1996 (27).

Hamilton Anxiety Rating Scale (HAM-A): The Hamilton Anxiety Rating Scale (HAM-A) was developed by Hamilton in 1959 to determine the level of anxiety as well as the symptom distribution (28). It is a 4 point Likert scale that evaluates both spiritual and physical symptoms. The Turkish validity and reliability study of the scale was conducted by Yazıcı et al. in 1998 (29).

Situational Awareness Test (SAtest): The SAtest is a dynamic visual tracking test that was developed on the basis of Endsley and Garland's Situational Awareness Global Assessment Technique (12) (18). In the SAtest, participants are asked to observe the locations, identities, and actions of 5 targets moving within a rectangle. The five targets consist of different images and are separated into 2 groups, such as insect and lizard groups. The insect group consists of an ant, fly, and spider, while the lizard

group is composed of turquoise and yellow lizards. The lizards follow an insect that is targeted by the computer program. If the lizard catches the target insect, the lizard "eats" that insect, and then tries to catch a new insect. During this dynamic simulation, the insects and lizards disappear from the screen at certain time intervals, and one of three stages of situational awareness is tested by displaying questions on the screen. To test SA1, participants are asked to identify the locations of all of the targets, while the identification of two targets in a given location on the screen is used to test SA2. The SA2 stage requires information integration between the target location and identity. To test SA3, participants are asked to determine the direction of the target at the bottom of the screen (Figure 3). The SA test consists of four blocks, with the exception of the practice section. In the practice section, the test is introduced by asking sample questions about SA 1, 2, and 3. The next 3 blocks contain 15 simulations each, and related questions are asked for SA 1, 2, and 3. In these three blocks, the participants know which questions they will be asked prior to watching the simulations. The fourth and final block consists of 15 simulations from each of the previous three blocks in a random order. As the participants watch the simulations in this block, they are unaware of the questions to follow. Thus, the first 3 blocks are "goal-driven," where attention is directed to the target, while the last block is "data-driven," which is driven by environmental cues. In addition, the 3 stages of the SA test are evaluated separately according to the accuracy and time parameters of these two blocks, namely goal-driven and data-driven. Lower scores (obtained with logarithms of the values related to accuracy) indicate a higher level of situational awareness. For detailed information about the test, we refer the reader to the following: Figure-1, reference (17), and <https://www.youtube.com/watch?v=zfFRQqFTC-Q>.

Figure 1. Situational Awareness Test (SAtest)

Table 1. Comparisons of SAtest scores of groups

SAtest scores	Mean±SD			Statistical analysis		
	OCD s=67	Relatives s=50	Controls s=41	F d.f.	p	MANOVA
SA 1						
Accuracy goal-driven	-0.249±0.11	-0.290±0.11	-0.308±0.10	3.832; 2	0.02	OCD<Control*
Accuracy data-driven	-0.157±0.08	-0.191±0.10	-0.205±0.08	3.933; 2	0.02	OCD<Control*
Time goal-driven	3.741±0.18	3.667±0.15	3.638±0.12	6.083; 2	0.003	OCD<Control* OCD<Control*
Time data-driven	3.770±0.15	3.723±0.14	3.707±0.13	2.777; 2	0.06	-
SA 2						
Accuracy goal-driven	-0.168±0.09	-0.179±0.07	-0.191±0.08	0.907; 2	0.40	-
Accuracy data-driven	-0.134±0.06	-0.142±0.06	-0.143±0.06	0.306; 2	0.73	-
Time goal-driven	3.778±0.17	3.729±0.15	3.692±0.09	4.479; 2	0.013	OCD<Control*
Time data-driven	3.788±0.18	3.737±0.14	3.708±0.11	3.632; 2	0.02	OCD<Control*
SA 3						
Accuracy goal-driven	1.861±0.10	1.803±0.16	1.822±0.12	2.973; 2	0.054	-
Accuracy data-driven	1.892±0.11	1.840±0.13	1.875±0.07	2.789; 2	0.06	-
Time goal-driven	3.731±0.14	3.689±0.16	3.669±0.13	2.564; 2	0.08	-
Time data-driven	3.718±0.15	3.699±0.15	3.655±0.11	2.516; 2	0.08	-

Statistical Analysis

All statistical analyses in this study were carried out with SPSS (Statistical Package for Social Sciences) version 22.0 for Windows. The Chi-square test was used to compare categorical variables and the One-Way ANOVA test was used to compare numerical variables between two groups. Correlations between the various clinical variables were investigated using the Pearson Correlation Test. The MANOVA test was used to analyze the findings of the SA test. The relationship between the situational awareness scores of the three groups and the clinical variables was assessed via partial correlation analysis (controlling for age and duration of education). A Bonferroni correction was used in all Post-Hoc comparisons. Values of $p < 0.05$ were accepted as significant for all tests.

RESULTS

In the OCD patient group, there were 51 females (76.1%) and 16 males (23.9%) with a mean age of 36.28 ± 11.87 years. In the first-degree relative group, there were 31 females (62%) and 19 males (38%) with a mean age of 37.86 ± 15.32 years, and there were 28 females (68.3%) and 13 males (31.7%) in the control group with a mean age of 35.76 ± 12.53 years. The mean duration of education was 10.27 ± 4.43 years, 11.34 ± 4.35 years, and 11.20 ± 3.60 years for each group, respectively. There was no significant difference among the three groups in terms of age, gender, and education level ($p > 0.05$ for all). In the OCD patients, the mean age of disease onset was 25.22 ± 10.53 years, the mean duration of disease was 11.05 ± 7.99 years, and the mean number of hospitalizations was 0.83 ± 1.76 . The mean Y-BOCS obsession and compulsion scores of the patients were 11.80 ± 4.66 and 10.85 ± 5.44 , respectively. When all three groups were compared in terms of MOCI subtests, HAM-D, and HAM-A scores, the scores of the OCD group were significantly higher compared to the first-degree relative and control groups, as expected ($p \leq 0.001$ for all).

Among the OCD patients, 19 patients were taking only an antidepressant (mean daily dose of fluoxetine 37.3 mg, fluoxamine 244.4 mg, sertraline 147.3 mg, paroxetine 43.3 mg, citalopram 40 mg, clomipramine 157.5 mg, venlafaxine 150 mg, duloxetine 60 mg, or mirtazapine 15 mg), and 46 patients were taking an antidepressant together with an antipsychotic (mean daily dose of aripiprazole 11.04 mg, quetiapine 191.9 mg, olanzapine 5 mg, risperidone 1.75 mg, haloperidol 2.5 mg, amisulpride

175 mg, or pimozide 1 mg). Two of the OCD patients were not taking medication.

The situational awareness scores of all three groups are summarized in Table 1. Analyses revealed that OCD patients had worse performance in SA in both the goal-driven and data-driven blocks as compared to controls. However, there were no significant differences among the groups in SA 2 and SA 3 in terms of accuracy.

When evaluating the relationship between situational awareness and obsessive-compulsive symptoms (controlling for age and duration of education) in the OCD group, it was found that there was no relationship between the SAtest performances and the Y-BOCS obsession and compulsion scores. Considering the obsession-compulsion subtypes, there was a positive correlation of both the goal and data driven phases of SA 1 with slowness and rumination ($r = 0.275, 0.307, 0.270, 0.353$, respectively; $p < 0.05$ for all).

DISCUSSION

The aim of this study was to compare situational awareness, which may be an endophenotypic marker in OCD, among OCD patients, their first-degree relatives, and controls. To our knowledge, this is the first study evaluating situational awareness in both OCD patients and their first-degree relatives.

There were statistically significant differences between the OCD patients and controls in both the goal-driven and data-driven tasks of the SA1 stage; however, there were no significant differences in the accuracies between the OCD patients and their relatives. Moreover, the first-degree relatives of OCD patients performed at a level between the controls and the OCD patients, particularly in the SA1 and SA2 stages (Figure 1). These findings partially support our hypothesis that the first stage of situational awareness (in particular) is an endophenotype for OCD.

The SA1 stage is only used to evaluate localizations of visual stimuli. There was a significant difference between the OCD patients and controls at this stage in our current study, suggesting that OCD patients might have more dysfunction in their lower-level cognitive functions in daily life. Our

Figure 2. Comparisons of SA1 and SA2 performances of the groups.

data was supported by the fact that previous visual and auditory evoked potential studies in OCD patients have also shown that OCD patients have disorders associated with early cognitive processing (30-33). On the other hand, our data indicate that there is a correlation between the SA1-stage performance of OCD patients and symptoms associated with slowness and rumination. This finding suggests that cognitive function disorders at lower levels of situational awareness may play a role in the development of obsessions and compulsions. In addition, these findings indicate that low-level cognitive functions should also be examined by investigators, who often focus on complex high-level cognitive functions as endophenotype candidates in OCD. Further studies in this field may provide valuable information that will help to elucidate the cognitive mechanisms of OCD. For example, it may be useful to investigate whether these unsure feelings/experiences of an event or action that is believed to play an important role in OCD phenomenology are associated with SA1-stage dysfunction (34). Although OCD patients can generally speculate that an action has been taken, they might have a feeling that this action is incomplete. This feeling may be due to the first stage disorders of situational awareness. In a previous study, Kim et al. reported that OCD patients exhibited biological motion perception disorders (35). In that study, black dots imitating human body movements were used, and it was found that OCD patients were less aware than controls in realizing that the movements of these points (representing the head, arm, leg, and body) were similar to human movements. Considering the findings of our current study, the biological motion perception disorders reported by Kim et al. may be related with disorders in the simultaneous perception of locations of moving objects. The argument that OCD patients focus only on a locale, rather than on the entire shape of the visual area, also suggests that these patients most likely focus only on a certain part of the moving objects, rather than on the whole (36).

Although both the OCD patients and their first-degree relatives performed more poorly than the controls on the tests in the SA2 and SA3 stages in our study, these differences were not significant. To our knowledge, there has been only one published study assessing situational awareness in OCD patients (17). Similar to the results of our current study, that study also found that OCD patients had disorder in the SA1 stage, and they also reported a correlation between SA1 performance

and some obsessive-compulsive symptoms. On the other hand, although the same study revealed that the OCD patients performed more poorly than the controls in the SA2 stage, this difference was not significant in our current study. The differences in the results between the two studies may be due to the heterogeneity of the OCD patients included in these studies. Similar to our current study, the previous study did not reveal a significant difference between the OCD patients and controls in the SA3 stage, and this was attributed to the poor performance of the controls (due to the extreme difficulty of the SA3 stage). For this reason, we suggest that future studies use the 4 target version of the SA test rather than the five target version in order to reduce workload and increase sensitivity when comparing the groups.

To our knowledge, there is no direct evidence about the brain structures that are associated with SA. However, evidence suggests that visual-spatial cognitive processing may be associated with the parieto-occipital region. Considering this evidence, along with published data indicating the presence of parieto-occipital hypofunction (in addition to fronto-striatal hyperactivation) in OCD patients (37) and the improvement of this hypofunction with treatment (38,39), suggest that SA disorders in OCD patients might be associated with the parieto-occipital region. Moreover, it has been reported that in addition to the OCD patients, their first-degree relatives also exhibited parietal hypofunctions during a visual-spatial task that had results different from those of healthy individuals (40). In our current study, we believe a similar mechanism may be the reason that the SA performance of OCD patients and their first-degree relatives was not different. Despite these conclusions, we suggest that further studies utilizing simultaneous functional imaging during the SA task are necessary in order to demonstrate the exact brain structures that are associated with these disorders seen in OCD.

One limitation of this study is that almost all of the OCD patients were taking medication. Although previously published studies have reported that cognitive disorders in OCD patients do not change with treatment, the findings of our study should be validated in OCD patients who are not taking medication (41).

In conclusion, results of this study indicate that the lower-level cognitive disorders tested with the first stage of situational awareness may be an endophenotype candidate for OCD. Moreover, these disorders may be associated with obsessive-compulsive symptoms.

Ethics Committee Approval: This study was approved by Pamukkale University Non-Interventional Clinical Research Ethics Committee with the decision no. 57285 dated 30.09.2014.

Informed Consent: Informed consent were obtained from the participants.

Peer-review: Externally peer-reviewed.

Author contributions: Concept – ST; Design – ST; Supervision – ST; Resource – ST, DT; Materials –ST, DT; Data Collection &/or Processing –DT, ST; Analysis&/or Interpretation – ST, DT; Literature Search – ST, DT; Writing Manuscript– ST, DT; Critical Review – ST.

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