Additional Information for *"High-Dose Glycine Treatment of Refractory Obsessive Compulsive Disorder and Body Dysmorphic Disorder in a 5-Year Period"* [1]

W. Louis Cleveland, Ph.D.

"An acquaintance with the particulars of life is the beginning of all science."
Gordon Allport

"Observe, record, tabulate, communicate. Use your five senses…Learn to see, learn to hear, learn to feel, learn to smell…"
William Osler

Addendum 1 (www.InformaticPsychiatry.org)

AD1.1. Introduction.

In this addendum, we present additional, secondary information on the behavioral phenotype of the subject described in the above publication. Further clarification of methodological issues is also presented.

In the publication [**1**] and in this addendum, we give a detailed presentation of the behavioral phenotype in the belief that the behavioral dimension of psychiatric illness is no less important than the molecular dimension and that it is valuable to present both in full detail. It has also been our intention:

1) T*o describe the behavioral phenomenology in sufficient detail to permit the reader to make his or her own assessments of diagnoses and changes in the intensity of illness."*

2) *To make it possible to evaluate the results of our study independently of diagnostic criteria, which have undergone substantial historical variation and which are likely to change in the future.*

3) *To contribute to the future definitions of glycine-responsive subtypes of OCD and BDD.*

   The identification of subtypes will make it possible to preselect subjects for future, placebo-controlled trials of glycine and thereby increase the chances for successful trials. As yet, we have no idea of the frequency of glycine-responders in these diagnostic categories. If the frequencies are small, trials could fail and discourage further studies. Therefore, we strongly favor preliminary studies to identify glycine-responsive subtypes before large, expensive placebo-controlled studies are done.

4) *To make it possible for others to use the behavioral phenomena from this study as heuristic motivations and constraints for the construction of molecular-level hypotheses.*

   Here we would reiterate that subtle features of behavior, namely the kinetics of exacerbations, played a major role in the development of the Hypo-NMDAR signal transduction hypothesis on which this study is based.

AD1.2. Further Specification of the Behavioral Phenotype.

AD1.2.1. OCD.

An important aspect of any description of OCD is a characterization of the degree of self-insight. Kozak and Foa note that clinicians experienced with OCD generally recognize that insight into the irrationality of obsessive-compulsive fears is situation dependent, being greater in nonthreatening conditions and absent or reduced under fear-activating conditions [**2**]. O's presentation appears to be congruent with this perspective. For example, O's parents report that when O's fears associated with the line-crossing obsession were intensified by environmental stimuli (e.g. news of a crime event in a sensitive area), it would be extremely difficult to convince him of the irrationality of his fears. At other times, O is reported by his father to have been able to appreciate that his fears were excessive and very

different from most other people. During the peak periods of the three major exacerbations, intensity of the line-crossing obsession is currently recalled by O and his father to have been much higher and self-insight lower.

With regard to autogenous obsessions, O appears to have had a higher degree self-insight. For example, in periods when such obsessions have been inactive (which is most of the time) or on the rare occasions when they have emerged with mild distress, he is reported to have clearly understood that they were abnormal and has expressed the fear that they might return in the severe form experienced during exacerbations. However, during acute episodes, which occurred during the three major exacerbations, O currently reports that rituals were sometimes done to make the violent imagery go away or to keep it from returning. Distraction maneuvers were also performed during exacerbations, when violent imagery was distressful. For example, O currently recalls that the in age-22 exacerbation he would move repeatedly and quickly from one place to another in his home in an effort to create a distraction from the violent imagery. At times of peak illness, O currently recalls that this maneuver could be done for multiple hours per day. In the age-22 exacerbation, O also reports a "fear of losing his mind" during episodes of violent imagery.

There is also evidence that O saw his illness as a whole (rather than specific obsessions or preoccupations) as clearly abnormal. For example, at age 21 just after the failure of olanzapine augmentation of paroxetine and at a time of further deterioration, O made the following diary entry: "*I never dreamed that I would be out of school at this age. What is this illness that has taken my life away from me? What is this illness?*" Thus, in spite of any limitations of insight into specific obsessions or preoccupations, O appears to have appreciated in a general way that he was ill.

AD1.2.2. BDD.

O and his parents report that once BDD emerged, it was continuously present in the sense that they never observed a single day in which O could look at an image of himself in a normal manner. O currently recalls that in the preglycine period, he continuously believed himself to be ugly, suggesting that BDD-related self-insight was less than that for OCD.

It is of interest that O is reported to have been frequently praised for his good looks from early childhood, with one grandmother repeatedly encouraging him to become a professional child fashion model. No facial defects were ever noted by O's parents. With regard to BDD-by proxy, it can also be noted that family members do not consider O to resemble either his mother or his father.

As indicated in the above description, BDD-related preoccupations and ritualistic behaviors were activated (or intensified) when O saw an image of himself. We note with interest that this is analogous to the reactive, OCD-related line-crossing obsession described in Section A.1.3 (Appendix) [**1**]. This similarity brings to mind the fact that BDD preoccupations were regarded by some early researchers as "obsessions" [**3, 4**].

In Section A.1.2 (Appendix) [**1**], we noted that in periods when O spent multiple hours per day "working on the mirror," he would report rare good impressions of his face interspersed among numerous disturbing impressions. During these periods, O repeatedly reported that he saw his face change its appearance. Here we note that this is reminiscent of the visual distortions of body parts reported in ketamine experiments with normal human subjects. A manuscript describing a more detailed analysis of this phenomenon is in preparation.

Another BDD-related symptom was a hair-loss preoccupation, in which O became concerned that he could detect hair loss by feeling his hair with his hand. Over periods of multiple years, no hair loss was visible to his parents.

AD1.2.3. Somatic Preoccupations.

O's somatic preoccupations represent a subtle, complex and nosologically challenging set of phenomena. In this addendum, we present additional details and analyze them in relation to published descriptions of ketamine-induced phenomena in normal individuals.

Joint discomfort is among the more prominent subjects of O's somatic preoccupations. O currently recalls that he first experienced and complained about joint discomfort at age 21. Diary records indicate that O attempted to demonstrate his joint abnormality by "cracking" his knuckles during a neurology consult at age 26. The neurologist reportedly responded by "cracking" his own knuckles and urged O to ignore what he described as a very common ability of no medical significance. However, shortly after this, O's primary care physician considered the joint laxity to be unusual and initiated orthopedic and genetic examinations, both of which found a mild connective tissue disorder. This example illustrates the difficulty of characterizing somatic preoccupations and emphasizes the importance of careful observation and analysis of the fine details of these symptoms.

Complaints about cold hands began at age 21 when mild Raynaud's disease was identified. In recent years, there have also been complaints about hot hands. O's father reports that there are times when O's hands are distinctly cooler than his upper arm and times when the opposite is the case. No clinician has ever considered these conditions (including the documented Raynaud's disease) to require treatment.

On a few occasions, O has suggested as an inference that his physical discomforts might be related to anxiety and has noted that they seemed to get worse in times of stress. At other times, his complaints appear to be linked with a concern that not enough has been done to investigate or treat his illness. For example, he has repeatedly complained that his SPECT scans and Raynaud's disease have not prompted any specific treatments for these conditions. When currently asked, he states that he does not consider his concerns to be excessive and he states that the central issue is the physical discomfort that interferes with his activities

Another example of a somatic preoccupation is found in the clear and concordant recollections by O and his parents of the occurrence at age 5 of what they referred to at that time as a "sock seam neurosis". The "sock seam neurosis" involved pronounced complaints of discomfort from the seam at the tip of his sock. We note that very similar complaints have been reported by some individuals with TS [**5**]. Another feature of some cases of TS is an aversion to light and sound [**5**], which was seen in O's case at various times in the preglycine period. Likewise, O's complaints about body temperature are reminiscent of the disordered thermal perception and thermal disregulation reported for some cases of TS [**6**].

AD1.2.4. Sensory Hypersensitivity versus Abnormal Salience Evaluation.

In Section A.1.3 (Appendix) [**1**], we describe O's somatic preoccupations as possible manifestations of "sensory hypersensitivity." This term may not be the best choice since it can be construed to refer to a *generalized* hypersensitivity. A distinctive feature of O's somatic preoccupations is that the putative hypersensitivity is usually focused, at any given moment, on a single stimulus. For example, in the case of the "sock seam neurosis," the sensitivity was only to the sock seam. None of the many other body-surface stimuli from other parts of clothing and other agents exhibited any signs of preoccupation. This pattern, in our view, is more suggestive of abnormal salience evaluation than a generalized hypersensitivity. This possibility is of great interest in relation to findings in ketamine experiments with normal human subjects.

In multiple ketamine experiments with normal human subjects, it has been observed that ketamine causes weak, normally insignificant background auditory and visual stimuli to become highly salient and thereby capture attention [**7, 8, 9, 10**]. For example, Ivar Øye and coworkers report that: "… alteration in hearing was characterized by preoccupation with certain presumably "unimportant" sounds like the ticking of a clock or the sound from a centrifuge. The test persons often reported that these sounds were louder than before and that shifting the attention to another sound required unusual "effort" [**8**]. In another example, a subject reported that music quietly playing in another room sounded inordinately loud --- "like a transistor radio implanted in (his) ear" [**7**].

In the above discussion, the focus has been on somatic preoccupations. However, we suggest that the obsessions of OCD and the preoccupations of BDD may also be reflections of abnormal salience at other, nonperceptual levels of mentation. For example, an obsession in the mind seems quite analogous to having a transistor radio implanted in one's ear canal. In both cases, attention is powerfully captured by a single focus to a degree that resists volitional efforts to shift attention. Also, in both cases, contextual information is either ignored or poorly attended.

In the past, experiments with ketamine and human subjects have been designed in response to the hypothesis that NMDAR inhibitors induce a schizophrenia-like state. On the basis of the above discussion, we suggest that future ketamine experiments be designed in ways that will favor the detection of OCD- and BDD-like phenomena. Although there are many reports of ketamine-induced disturbances in body perception, to our knowledge, there are no reports of responses to face perception in mirrors, an experimental maneuver that would immediately be implied if one were to design experiments from a BDD (rather than from a schizophrenia) perspective. Here one is reminded of a famous statement by Albert Einstein:

> *"Whether you can observe a thing or not depends on the theory which you use. It is the theory which decides what can be observed."*

AD1.2.5. Commentary on NMDA Receptor Complexity.

In Sections 3.3 and 4.5 [**1**], we presented the Hypo-NMDAR signal transduction hypothesis without acknowledging the complexity of the NMDA receptor family in order to avoid an unduly long discussion. Here we wish to note that the NMDA receptor family contains multiple subunits (NR1A, NR1B, NR2A, NR2B, NR2C, NR2D, NR3A, NR3B) which are differentially distributed in the brain and which have different affinities and responses to glycine. Moreover, NMDARs may be intrasynaptic or extrasynaptic [**11**] and are thought to form NR1NRxNR1NRx heterotetrameric structures [**12**]. A more detailed description of the Hypo-NMDAR signal transduction hypothesis that considers this complexity is in preparation.

AD1.3. Further Specification of Methodological Procedures.

AD1.3.1. Selection of Data for Publication.

Given the very large amount of information in our subject's archive, any presentation in a publication necessarily represents a selection from available data. How this selection was made is an important methodological issue.

In our analysis of illness, we searched for any manifestations associated with impairment and/or distress, not just those expected for OCD and BDD and not just those seen in the preglycine period. All signs or reports of impairment and distress were investigated in relation to inner mentation and environmental context. In this investigation, we considered the possibility that some symptoms could be hidden because of their inherent nature (e.g. mental rituals) or because of embarrassment (e.g. symptoms relating to sexual matters). The possibility that symptom reports represented malingering or reflected a need to assume the sick role was also considered.

In selecting examples for publication, we gave emphasis to objective and qualitative changes in behavior that were sustained over time. An example of such a change is the resumption of barbershop haircuts. This improvement was a clear qualitative change that was sustained through all treatment and nontreatment periods. By focusing on sustained changes, we avoided reporting transient fluctuations in illness, which were judged to be of questionable significance. Except for two examples of mirror tolerance, which were clearly labeled as isolated events, all gains described were sustained, unless they were an aspect of a described relapse in a period of nontreatment.

AD1.3.2. Classification of Archival Information.

The complex spectrum of information in O's archive has led us to develop a formal classification scheme in which information is sorted into categories on the basis of the types of evidence that support it. This classification scheme is shown in Table 1.

Table 1: Classification of Archival Information

Category/Example	Description
1	**Reports from O and/or his parents describing objective phenomena that are corroborated by objected evidence from disinterested or blinded third parties or independent reports from third parties**
Example	There is a report that O attended an SAT preparation course. This report is corroborated by practice test reports from the course and records for credit card payments of course fees.
2	**Reports describing objective phenomena without additional corroboration**
Example	There is a report that O was taken by taxi to the SAT preparation course by his mother.
3	**Reports describing subjective evaluation of objective phenomena with corroboration by third-party objective evidence**
Example	There is a report from O's father that math performance in a tutoring session in OP6 was much improved over performance in eighth grade. This report was corroborated by results from a college placement test taken the day after the tutoring session.
4	**Reports describing subjective evaluation of objective phenomena with corroboration by third party subjective evidence**
Example	There is a report from O's father that O had difficulty maintaining eye contact during greetings. A physician's report from the same time period noted the same phenomenon.
5	**Reports describing subjective evaluation of objective phenomena without corroboration by third party evidence**
Example	There is a report from O's parents that O's room became extremely untidy in OP10.
6	**Reports describing subjective phenomena**
Example	There are O's reports about body sensations.

Evidence in Category 1 is, of course, more reliable than that in the other categories. However, we suggest that the reliability of evidence in Categories 2-6 varies considerably. For example, Category 2 evidence in our view is much more likely to be accurate and reliable than Category 6 evidence. Therefore, in our view, it is useful to consider these categories separately.

Although evidence in Categories 2-6 is less reliable than that in Category 1, we suggest that it is valuable since it generates a more complete picture of our subject and of the events that occurred during periods of glycine treatment and nontreatment. We also suggest that it will be useful to others attempting to replicate our findings. Moreover, an experienced observer of OCD and BDD will be able to evaluate this information for its reasonableness in relation to the known features of these disorders. Readers will also be able to evaluate this evidence for its internal consistency and its consistency with Category 1 evidence. From our perspective, the secondary evidence in Categories 2-6 is a useful complement to the primary evidence in Category 1 that contributes to the informativeness of our publication. However, our

main evidence for the *efficacy* of glycine is in Category 1 not in Categories 2-6 as discussed in detail in Section 4 [**1**].

AD1.3.3. Recommendations for Routine Monitoring of High-Dose Glycine Therapy.

In the absence of systematic studies, it seems prudent to monitor both plasma ammonia and brain glutamine (in addition to liver and kidney functions) in individuals who are currently receiving glycine treatment, especially long-term treatment. Such monitoring would be particularly important if glycine is used with other reagents, such as sodium valproate, which may independently induce hyperammonemia [**13**].

It should be appreciated that different commercial laboratories may use different HPLC methods for assay of plasma amino acids and that noticeably different results may be obtained with the different methods. Comparisons of changes in plasma amino acids over time should therefore be done with measured values obtained with the same technique. For the results presented in this study, the commercial diagnostic laboratories reported that the Pico Tag method from Waters was used.

It should also be appreciated that artifactually high values for plasma ammonia are frequently obtained from commercial diagnostic laboratories as a result of inappropriate techniques for phlebotomization. Phlebotomization by properly trained personnel is therefore essential. Moreover, to confirm possible hyperammonemia, orotic acid should be measured on a urine sample obtained at the same time blood for plasma ammonia is collected.

AD1.3.4. Glycine Ingestion.

Glycine is unpalatable and generates considerable taste revulsion. It was usually taken as a slurry in orange juice. Aliquots of milk were interspersed between aliquots of slurry to reduce taste revulsion. See Table 1 for amounts [**1**]. O has been repeatedly queried by his father regarding body sensations during and after glycine consumption. Rarely, slight nausea can be felt, but this disappears immediately after consumption. Slight somnolence immediately after consumption is reported to have been experienced on rare occasions. O currently recalls that unpalatability causes him to ingest larger doses of glycine slowly, e.g. in a period as long as 30 minutes.

AD1.3.5. Methodological Implications for Future Microbehavioral Studies.

One might conclude that the microbehavioral approach [**14, 15**] for personalized research used in this study cannot be widely employed, since it depends on the availability of personal archives that require very time- and labor-intensive efforts to assemble and analyze. We suggest that this is not the case, since automated monitoring of abnormal OCD and BDD microbehaviors may become possible in the near future.

The possibility of automated microbehavioral monitoring has recently arisen as a result of major advances in sensor technology, in pattern recognition algorithms (e.g. the soft margin support vector machine [**16**] with recent improvements in training algorithms [**17**]) and in communications technology (cell phone networks and the internet). This study is currently being used as a prototype for guiding the development of the software and sensor technology that will make automated microbehavioral studies a practical reality (manuscript in preparation).

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