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Research report

Parallels between behavioral and neurochemical variability in the rat vacuous chewing movement model of tardive dyskinesia

Susan E. Bachus[a,b,*], Elizabeth Yang[b], Sara Sukontarak McCloskey[a], Julie Nealon Minton[a]

[a] Department of Psychology, St. Mary's College of Maryland, 18952 E. Fisher Rd., St. Mary's City, MD 20686-3001, USA
[b] Department of Psychology, 2024 David King Hall, George Mason University, Fairfax, VA 22030, USA

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ABSTRACT

The widely accepted rat vacuous chewing movement model for tardive dyskinesia could be more fully mined through greater focus on individual variability in vulnerability to this neuroleptic-induced behavior. We have examined parallels between behavioral and neurobiological variability within a cohort in order to evaluate the role that neurobiological factors might play in determining susceptibility to tardive dyskinesia. Inter-observer reliability and individual consistency across time, in both spontaneous and neuroleptic-induced vacuous chewing movements, were empirically demonstrated. While this behavior increased across 8 months of observation in both vehicle controls and haloperidol-treated rats, pretreatment baselines were predictive of final levels across individuals only in the vehicle control group, not the haloperidol-treated group. Haloperidol-induced elevations in neostriatal D2 and GAD_{67} mRNA were not correlated with individual variability in haloperidol-induced vacuous chewing movements. Ambient noise during the observations was found to exacerbate chronic haloperidol-induced, but not spontaneous vacuous chewing movements. Significant correlations were found among the haloperidol-treated rats between nigral and tegmental GAD_{67} and tegmental $\alpha 7$ mRNA levels, measured by in situ hybridization histochemistry, and vacuous chewing movements, specifically in the noisy conditions. Variability in these secondary responses to primary striatal dopamine and GABA perturbations may play a role in determining vulnerability to vacuous chewing movements, and by analogy, tardive dyskinesia. Both the differential predictive value of baseline vacuous chewing movements and the differential effect of noise, between controls and haloperidol-treated rats, add to evidence that haloperidol-induced vacuous chewing movements are regulated, in part, by different mechanisms than those mediating spontaneous vacuous chewing movements.

1. Preface

So pervasive has been the fabric of Philip Teitelbaum's influence on subsequent generations of behavioral neuroscientists, that it is difficult to tease apart the strands. He has always been adamant that "psychology is a science that will endure in its own right" [1] and has been instrumental in ensuring this status for our field. He proudly argued that we should not deign to serve as "handmaidens" to the other neurosciences, providing "behavioral bioassays" for drug screening for pharmacologists, but should study behavior in its own right. The vacuous chewing movement model for tardive dyskinesia, utilized in this study, has been described by its founder as useful for "monitoring the risk of tardive dyskinesia with individual drugs" [2] and for "developing drugs for the treatment of facial dyskinesias in humans" [3]. Yet those applications risk falling into the role of handmaiden that Philip warned us against. The goal in the use of the model here has been to, instead, harness neuroanatomy and neurochemistry to serve as tools for exploration of the neurobiological substrates that determine individual variability in this behavior, and by analogy, tardive dyskinesia.

Nevertheless, though he argued that "As physiological psychologists, our primary scientific responsibility is to build psychology, not medicine" [1], Philip also presaged the current "from bench to bedside" mentality in contemporary neuroscience with his conviction that behavioral studies could be equally well applied to the understanding of pathology [4,5]. Moreover, individual differences in behavior should be noted and considered (e.g. [6]), not swept under the rug or rejected as "outliers". Finally, Philip exhorts us [1] that we must use analysis and resynthesis in psychology, to avoid the pitfall of reductionism. Our attempt here has been to dissect apart, and then reintegrate, neuroanatomically and neurochemically specific pieces of a larger puzzle, in the hope of elucidating the

* Corresponding author at: Department of Psychology, 2024 David King Hall, George Mason University, Fairfax, VA 22030, USA. Tel.: +1 703 250 2581; fax: +1 703 250 2581.
E-mail addresses: sbachus@gmu.edu, susanbachus@verizon.net (S.E. Bachus).

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behavior at hand, rather than settling for using it for screening purposes. For this special issue, commemorating Philip's Festschrift, in clinical relevance, delving into historical literature, following unexpected behavioral observations, attending to individual differences, and attempting to "resynthesize" neuroanatomically and neurochemically specific elements, in the service of better understanding determination of behavior, this study has endeavored to conform to tenets he espoused, which have shaped, and continue to guide, the evolution of the field of behavioral neuroscience.

2. Introduction

Within a decade of the advent of treatment of schizophrenia with neuroleptic drugs, concern had arisen that severely disabling, and sometimes extremely persistent, if not irreversible bucco-lingual-masticatory involuntary movements, emerged in a subpopulation of patients treated with these drugs after a long latency of months or years [7–11]. Due to this long latency, this debilitating side effect has come to be referred to as tardive dyskinesia. Though second generation neuroleptics known as "atypical" have been found not to induce tardive dyskinesia [12], "a trend toward greater improvements in Quality of Life Scale and symptom scores" [13] for schizophrenic patients treated with first generation neuroleptics, relative to atypicals, has been demonstrated. Many patients who are not at risk for developing tardive dyskinesia might be more effectively treated with the classical neuroleptics. Thus, determining the factors that produce vulnerability to tardive dyskinesia in some patients remains an important goal for the treatment of schizophrenia. Our focus has been on exploring individual variability in the rat vacuous chewing movement model of tardive dyskinesia, in both behavioral and neurochemical measures, to evaluate whether correlations between behaviors and neurochemical markers might implicate neuroanatomically- and neurochemically-specific effects of chronic haloperidol in the mediation of the behavioral changes.

Early speculation that tardive dyskinesia might be caused by development of compensatory supersensitivity of striatal D2 dopamine receptors (at the time called "dopamine-facilitated receptor"[s]) [14] initially seemed supported by evidence in animals of potentiated behavioral responsiveness to dopaminergic agonists [15–17]. However, discrepancies have argued against the interpretation that dopaminergic supersensitivity alone could explain the pathology. Patients with and without tardive dyskinesia do not differ for measures of D2 receptor binding at post-mortem [18,19], and, in patients withdrawn from neuroleptics, tardive dyskinesia persists after withdrawal from neuroleptic medication, despite striatal D2 receptor binding levels, measured in vivo, that do not differ from those of patients without tardive dyskinesia, or non-schizophrenic controls [20,21].

By patiently observing rats treated with neuroleptics for several months, without introducing any stimulant challenge, several investigators found that oral dyskinesias (dubbed "vacuous chewing movements" because the behavior resembles chewing except that the mouth is empty) emerged in some rats [22–25]. Not only is this behavior more similar to tardive dyskinesia than stimulant-induced stereotypies in its orofacial topography, but it more closely parallels tardive dyskinesia in its long latency, persistence after neuroleptic discontinuation, and high variability in occurrence across individuals, than the stimulant-induced stereotyped behaviors studied earlier, and has supplanted them as the most common animal model for tardive dyskinesia (reviewed in [26]). It has been empirically demonstrated that counts of these chewing movements that can be easily made by human observers are in close accord with computerized measurements of relative movements of fluorescent spots painted on the rat's upper and lower jaw [27]). Two distinctions are important: (1) "Early onset" vacuous chewing movements can also be induced by relatively acute neuroleptic treatment (<28 days), that are pharmacologically and neurochemically different from those emerging slowly during chronic treatment [28]. (2) Route of administration is critical. Mouth movements produced by exposure through drinking water did not persist after neuroleptic discontinuation in some studies [29,30] (although those in another study did [25]), in contrast to those produced by long-acting decanoate depot intramuscular injection (e.g. [24]). Thus, the focus here will be on chronic (>28 days) exposure through depot administration.

Perhaps the most potentially valuable aspect of the vacuous chewing movement model is the high individual variability, which might serve as a handle for exploring possible determinants of vulnerability to tardive dyskinesia. Thus, it seems ironic that it is quite typical in studies using this model for both vacuous chewing movements and various neurobiological measures to be collected, without any evaluation of the relationship between these measures [28,31–33]. In some studies a comparison was made for neurobiological measures between subpopulations of rats that are classified as "high" or "low" for vacuous chewing movements (e.g. [34–41]), but even this approach seems to fail to fully exploit the data collected. Though a seminal study by Gunne and Häggström [42] described a significant negative correlation between vacuous chewing movements and nigral glutamic acid decarboxylase (GAD) activity, across individuals, subsequent studies have very rarely similarly explored parallels between behavioral and neurochemical variability through correlations. (One failure to find a significant correlation may have been due to relatively short treatment, in one group, and long withdrawal in another [43]). Admittedly, neither correlations nor naturally occurring subpopulations establish causality, but they can still serve as powerful suggestive indicators to guide working hypotheses that specific neurobiological substrates or factors might contribute to the determination of individual susceptibility to tardive dyskinesia, which can then be tested experimentally.

Our aim here has been to carefully characterize individual variability in both behavioral and neurochemical variables in a large cohort, both in baseline levels and during chronic exposure to haloperidol decanoate or vehicle control. Long-Evans rats were selected because this strain has been found to have both high levels and high variability in both baseline and neuroleptic-induced vacuous chewing movements [44]. We also explored parallels between behavioral and neurochemical variability, by utilizing in situ hybridization histochemistry to measure regionally specific mRNAs in the post-mortem brains from this cohort. One advantage to a histochemical approach to such biological measurements is that numerous thin sections can be generated from a single brain to be utilized for such studies (see [45] for discussion of this methodology). Our initial focus for this effort has been on the primary locus of neuroleptic effects at the D2 receptors in the neostriatum, and on the GABA-synthetic enzyme glutamate decarboxylase 67 (GAD_{67}) found in D2 receptor-positive GABA neurons in the neostriatum, and on the nigrotegmental GABAergic outflow to the vicinity of the pedunculopontine nucleus, which we have previously implicated in the mediation of vacuous chewing movements [46]. We also examined choline acetyltransferase and $\alpha 7$ receptors, which are co-localized in the cholinergic neurons of the pedunculopontine tegmentum [47], which has been shown to receive direct dopaminergic innervation [48], because of a long history of evidence (e.g. [49]) that cholinergic pathology may also contribute to the etiology of tardive dyskinesia.

Additional potentially interesting factors became apparent after behavioral observations commenced, thus were added into the experimental design: (1) We noticed that vacuous chewing movements often seemed to spike in response to noises in the