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Forecasting remission from the psychosis risk syndrome with mismatch negativity and P300: Potentials and pitfalls

Holly K. Hamilton^{1,2}, Brian J. Roach^{1,3}, Daniel H. Mathalon^{2,1}

¹San Francisco VA Health Care System, San Francisco, CA

²University of California, San Francisco, San Francisco, CA

³Northern California Institute for Research and Education, San Francisco, CA

Abstract

Clinical outcomes vary for individuals at clinical high risk (CHR) for psychosis, ranging from conversion to a psychotic disorder to full remission from the risk syndrome. Given that the majority of CHR individuals do not convert to psychosis, recent research efforts have turned toward identifying specific predictors of CHR remission, a task that is conceptually and empirically dissociable from identification of predictors of conversion to psychosis, and one that may reveal specific biological characteristics that confer resilience to psychosis and provide further insights into the mechanisms associated with the pathogenesis of schizophrenia and those underlying a transient CHR syndrome. Such biomarkers may ultimately facilitate the development of novel early interventions and support the optimization of individualized care. In this review, we focus on two event-related brain potential measures, mismatch negativity (MMN) and P300, that have attracted interest as predictors of future psychosis among CHR individuals. We describe several recent studies examining whether MMN and P300 predict subsequent CHR remission and suggest that intact MMN and P300 may reflect the integrity of specific neurocognitive processes that confer resilience against the persistence of the CHR syndrome and its associated risk for future transition to psychosis. We also highlight several major methodological concerns associated with these studies that apply to the broader literature examining predictors of CHR remission. Among them is the concern that studies that predict dichotomous remission vs. non-remission and/or dichotomous conversion vs. non-conversion outcomes potentially confound remission and conversion effects, a phenomenon we demonstrate with a data simulation.

Corresponding Authors: Holly K. Hamilton PhD (holly.hamilton@ucsf.edu), Daniel H. Mathalon, PhD MD (daniel.mathalon@ucsf.edu), Department of Psychiatry & Behavioral Sciences, University of California, San Francisco.

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Keywords

electroencephalography; mismatch negativity; P300; clinical high risk for psychosis; remission; schizophrenia

Observations that a shorter duration of untreated psychosis predicts better clinical outcomes (1) has led to international efforts to understand the early phases of psychotic disorders. In support of these efforts, clinical criteria have been developed for identifying individuals who are at “clinical high risk” (CHR) for developing psychosis, also known as the “psychosis risk syndrome” or “at-risk mental state” (2–5). These CHR criteria generally include the presence of attenuated positive symptoms, brief intermittent full psychosis symptoms, and/or recent deterioration in functioning with genetic risk for psychosis (2–5). Using these criteria, researchers can prospectively identify and follow individuals considered to be at risk with the goal of clarifying pathogenic mechanisms associated with psychosis onset.

While algorithms using clinical and cognitive data to predict future conversion to psychosis among CHR individuals have now been developed and validated (6,7), they are not yet sufficiently accurate to support major treatment decisions in the clinic. Accordingly, recent research has focused on identifying biomarkers that precede psychosis onset, and major advances have been made in identifying electrophysiological (see 8,9,10), neuroimaging (see 10,11), and other biological markers (12,13) that are associated with future conversion to psychosis among CHR individuals.

Although the validity of CHR criteria for predicting future risk for psychosis has been demonstrated (14), the 40–50% psychosis conversion rate initially reported when the CHR paradigm was developed (15) has since declined substantially (14), with recent estimates indicating a rate of 22–36% within two to three years of ascertainment (6,14,16–19). According to meta-analysis, 73% of CHR individuals do not convert to psychosis within two years, and approximately 43% fully remit from the CHR syndrome (20). Given the range of clinical outcomes among CHR individuals and the fact that most do not transition to psychosis, recent efforts have turned toward identifying specific predictors of CHR remission in addition to markers of future psychosis conversion.

Indeed, there are several advantages to focusing on predictors of remission among CHR individuals. Importantly, the identification of biomarkers that can reliably distinguish future CHR remitters from nonremitters may reveal specific characteristics that confer resilience to psychosis and provide further insights into the mechanisms associated with both the pathogenesis of schizophrenia as well as those underlying transient attenuated psychosis symptoms. Such biomarkers may, in turn, also help to identify more precise, mechanistically informed treatment targets, facilitating the development of novel early interventions. In addition, the ability to distinguish future remitters from those whose symptoms are likely to persist would benefit future clinical trials; enriching trial samples for psychosis risk by screening out CHR individuals most likely to remit would minimize the likelihood of inflated placebo effects or even false positive results (21). Furthermore, biomarkers that predict clinical remission may ultimately support efforts to develop staged treatment algorithms, ultimately providing an opportunity for the optimization of individualized care.

While current efforts to identify predictors of CHR remission are examining a range of biomarker, neurocognitive, and/or clinical measures, the goal of the current article is to review studies that have specifically assessed electroencephalography (EEG)-based event-related potential (ERP) measures. ERP components, which reflect voltage fluctuations in EEG scalp-recordings time-locked to specific task stimuli, have several attractive features as potential predictive biomarkers of CHR outcomes, including their low-cost, high temporal resolution, and translational links with homologous electrophysiological signals recorded in animal models. Here, we specifically focus on two ERP measures, mismatch negativity (MMN) and P300, that have been the major focus of EEG-based CHR remission studies to date, likely because they were already shown to predict conversion to psychosis (e.g., 22,23–26), and because of the substantial prior literature documenting their deficient amplitudes in schizophrenia (e.g., 27,28–30).

In addition to reviewing the MMN and P300 CHR remission studies published to date, we highlight methodological issues illustrated by these studies, many of which are applicable to the broader literature and inform our recommendations for best practices for future studies. One of these issues, the confounding of prediction of remission with prediction of conversion effects, is identified as a major concern that arises in most studies examining a wide range of predictors of CHR remission. We also provide a data simulation to demonstrate how these confounds arise when CHR individuals are dichotomized as remitters or non-remitters based on their clinical outcomes while including converters among the non-remitter group.

MMN and P300 as Predictors of CHR Remission

Mismatch Negativity

Auditory MMN is a negative voltage, frontocentrally-distributed, ERP component elicited automatically between 100–250ms following infrequent deviant sounds interspersed among frequent “standard” sounds (31–33). Deviance in any number of sound features (e.g., pitch, duration, intensity) can elicit MMN (32). MMN generators have been localized to regions of auditory and frontal cortex (33,34) and it is considered to be at least partially mediated by glutamatergic neurotransmission at N-methyl-D-aspartate receptors (NMDARs) (35–37). MMN reflects automatic feature analysis involving a form of sensory echoic memory (31,38) and also reflects longer-term neural plasticity (39) and auditory predictive coding (40–42). MMN is largely unaffected by top-down processes (31,43,44), allowing the examination of auditory processing without the confounding influence of attention and motivation (45). Deficient MMN has been well-documented in schizophrenia (27,28) and is sensitive to cognition (46–49) and functional outcomes (50,51). Several studies have also reported that reduced MMN amplitudes are associated with greater future risk for psychosis conversion (22,52–55) and shorter time to conversion (22,23) among CHR individuals.

Two studies have examined whether MMN predicts future CHR remission. In 48 CHR individuals and 47 healthy controls (HCs), Kim and colleagues (56) examined whether duration-deviant MMN predicts prognosis among CHR individuals followed clinically for up to 6 years by comparing baseline MMN amplitudes across CHR remitter (n=17), non-remitter (n=31), and HC groups. CHR remission was defined according to the Scale of

Psychosis Risk Symptoms (SOPS) criteria (2); that is, receiving a rating of “mild” or lower on all positive symptom subscale items, as well as a score 60 or higher on the Global Assessment of Functioning (GAF) scale (57). Non-remitters included 7 individuals who converted to psychosis and 24 individuals who continued to meet CHR criteria during the study follow-up period. CHR remitters and HCs did not differ in baseline MMN amplitude, and both groups had larger MMN amplitudes than the CHR non-remitters. Moreover, larger MMN amplitudes predicted a greater likelihood of being a remitter in a logistic regression analysis. Greater MMN amplitude also predicted functional recovery and was associated with improved SOPS positive symptom ratings after adjusting for antipsychotic medication dosage and years of education.

Fujioka et al. (58) examined whether duration-deviant and pitch-deviant MMN predicts CHR remission and cognitive function. Twenty-four CHR participants were followed for at least 6 months, at which point clinical status and neurocognitive function were assessed. CHR remission was defined by both symptomatic and functional improvement, indicated by SOPS positive symptom subscale scores and the GAF score (61). The non-remitter group (n=18) comprised individuals who continued to meet CHR criteria (n=15) and those who converted to psychosis (n=3). The amplitude of duration-deviant MMN, but not pitch-deviant MMN, was greater in the remitter (n=6) than the non-remitter group, while only pitch-deviant MMN together with the SOPS positive subscale score predicted scores on a measure of attention (59) at follow-up.

P300

P300 is a positive voltage ERP component typically elicited during auditory or visual oddball target detection tasks by behaviorally relevant or salient infrequent stimuli interspersed among “standard” stimuli (60). P300 amplitude is posited to reflect attentional resource allocation (60–62), contextual updating of working memory (63,64), and stimulus salience processing (65,66). There are two subcomponents of P300 that are elicited under specific task conditions. P3b, which is maximal over parietal scalp electrodes, is elicited by infrequent target stimuli that participants are asked to detect and that require a response (e.g., button press, count). P3a, which occurs approximately 50ms earlier than P3b and is maximal over frontocentral electrodes, is elicited by infrequent novel or otherwise salient non-target distractor stimuli that require no response (60). P3b reflects effortful top-down attentional allocation, whereas P3a reflects automatic, bottom-up orienting of attention (60,67). P300 generators have been primarily localized to prefrontal cortex (P3a) and temporal-parietal junction (P3b) (68). Like MMN, P300 depends on NMDAR neurotransmission (69), but noradrenergic (70), dopaminergic (60), GABAergic (71), serotonin 5-HT_{2A} (72), cholinergic muscarinic (73) and cannabinoid receptors (74,75) may also be involved. Both target P3b and novelty P3a amplitude reductions are well-established in schizophrenia, especially during auditory tasks (29,30,76). Some studies have also shown that P300 amplitude fluctuates with clinical state (77,78) and that abnormalities worsen with longer illness duration (79,80).

A number of studies have consistently reported that auditory and visual target P3b is associated with future conversion to psychosis among CHR individuals (24–26,81), and that

smaller P3b amplitudes predict the imminence of conversion (24–26). In contrast, CHR studies of novelty P3a have yielded mixed results, with some (82), but not others (25,26,83) reporting deficient baseline P3a amplitudes in future CHR converters relative to non-converters. P3a has not been shown to predict time-to-conversion (25,26).

Several studies have asked whether P300 amplitudes are associated with CHR remission. Kim et al. (84) examined whether baseline auditory target P3b, measured during a two-stimulus (targets, standards) auditory oddball paradigm, predicted remission from the CHR syndrome in 45 CHR individuals followed clinically for at least two years. Based on clinical outcomes, CHR individuals were classified as having achieved full symptom remission (n=19) or having persistent attenuated psychotic symptoms *without* converting to psychosis (n=26). Remission was defined by SOPS positive symptom scores and GAF score (< 60). There were no differences in baseline target P3b between CHR remitters and CHR individuals with persistent symptoms but larger baseline P3b amplitude predicted subsequent improvement in SOPS negative and general symptoms.

In another study, approximately 130 CHR and 69 HC participants completed two auditory oddball tasks that involved counting target tones (82). P3b amplitudes to target tones were measured during a two-stimulus (targets, standards) paradigm and P3a amplitudes to novel stimuli were measured during a three-stimulus (targets, novel sounds, standards) paradigm. After one year of clinical follow-up, CHR individuals were categorized into psychosis converters, individuals who continued to meet CHR criteria, and those who met SOPS positive symptom subscale remission criteria. Novelty P3a amplitudes of the CHR remitter group (n=68) at baseline were similar to the HC group (n=69) and were greater than CHR converters (n=23) and CHR individuals whose syndrome persisted (n=40). Target P3b amplitude was also reduced in CHR converters (n=19) relative to remitters (n=53).

Finally, an analysis of P300 data from the large North American Prodrome Longitudinal Study (NAPLS-2) examined whether baseline target P3b and novelty P3a amplitudes are associated with future conversion and remission outcomes among CHR individuals who were followed for at least two years (25). CHR (n=552) and HC (n=236) participants completed a three-stimulus (targets, novels, standards) auditory oddball task in which participants pressed a button in response to target tones. Baseline P300 amplitudes were compared between CHR converters (n=73) and CHR non-converters, defined as having been followed for 24 months and either continuing to meet CHR criteria (n=135) or meeting SOPS remission criteria (n=90).

While target P3b amplitude was reduced among converters relative to the whole non-converter group, further analysis demonstrated that CHR remitters had baseline target P3b amplitudes that were equivalent to HC and were greater than both the CHR individuals with a persistent CHR syndrome and the CHR converters to psychosis. In contrast, novelty P3a amplitude at baseline did not differentiate future CHR remitters from persistently CHR individuals or from psychosis converters.

Summary

Although most prior CHR studies that have followed individuals longitudinally have examined whether baseline neurophysiological abnormalities predict future psychosis, this review highlights recently emerging evidence from several independent studies suggesting that both MMN and P300, which are known to be abnormal in schizophrenia, not only predict conversion to full psychosis but are also associated with future remission among CHR individuals. Specifically, these studies provide initial evidence that relatively normal amplitudes of MMN and P300 at the time of CHR diagnosis may be associated with future CHR remission and/or improvements in functional status. Together, these initial studies implicate MMN and P300 as possible neurophysiological manifestations of pre-attentive and attention-mediated neurocognitive functions or neuroreceptor processes that confer resilience against persistence of the CHR syndrome and its associated risk for psychosis onset. Interestingly, both MMN and P300 rely on contextually-derived expectancies and stimulus probabilities, such that both show greater amplitudes to improbable events when the deviant stimulus is preceded by longer sequences of standard stimuli (85,86). Relatively normal MMN and P300 amplitudes among remitters relative to CHR individuals with a persistent syndrome suggest that both intact predictive coding and top-down attentional control processes may support future CHR remission and may even promote improvement in CHR symptoms. Moreover, given the dependence of MMN on glutamate NMDAR neurotransmission, as well as the involvement of NMDARs in P300 generation (69), intact MMN and P300 among future CHR remitters may reflect relatively normal NMDAR function that confers resilience against persistence of CHR symptoms or progression to full psychosis (e.g., see 87,88–90).

Methodological Issues Regarding ERP Studies Predicting CHR Remission

The small literature suggesting a role for MMN and P300 as predictors of CHR remission is associated with several methodological limitations. First, given the relatively small samples of CHR remitters examined in most of the studies to date, more large-scale studies are needed to definitively determine the predictive value of these measures. Second, the paradigms used to assess MMN and P300 differed across studies; differences in task instructions and the type and probability of stimuli used complicate direct comparison of results. Broad adoption of standard paradigms for eliciting MMN and P300 can be achieved in large multi-site studies but reaching convergence of paradigms across independent labs is far more challenging. Third, studies differed in the scalp electrode sites analyzed, the EEG preprocessing and data cleaning pipelines implemented, and the methods used to extract the signals of interest. Efforts to standardize electrode montages, data preprocessing pipelines, and ERP component measurement approaches would further facilitate comparisons across studies. At the same time, it may still be premature to foreclose on the possibility that novel and more sophisticated EEG processing pipelines and measurement approaches will yield measures that more accurately predict CHR remission.

General Methodological Issues Associated with Studies Predicting CHR Outcomes

Importantly, the ERP literature reviewed here also highlights several critical methodological issues that apply across all studies aimed at prediction of CHR remission, irrespective of the type of predictor examined.

Variable definitions of remission and the need for a standard definition

Criteria and measures used to define CHR remission have varied across studies, limiting direct comparisons of their results. Current CHR diagnostic systems have paid relatively little attention to classification at follow-up for outcomes other than psychosis conversion (91). While some CHR studies define remission as an attenuated positive symptom score (e.g., SOPS score) below the CHR threshold, others have additionally required functional remission. Whether to incorporate functional status in CHR remission criteria is an important consideration, as a previous study found that 56% of CHR participants were classified as remitters based on symptomatic improvement after one to two years of follow-up, but that the proportion of remitters in the sample declined to 40% when functional improvement was also required (92). In addition, while some have defined functional remission based on a single cutoff score, other studies, including NAPLS (91), have defined functional improvement in relation to an individual's premorbid level of functioning.

Documenting remission with greater temporal granularity

While many studies have utilized time-to-event analyses such as Cox regression to examine whether baseline clinical variables predict the imminence of psychosis onset, no studies have attempted to predict time-to-remission. In order to evaluate predictors of time-to-remission in a manner similar to predictors of time-to-conversion, CHR outcomes need to be assessed with greater temporal granularity. While conversions to psychosis that occur between longitudinal assessments are often reported to the research team as they occur, or are straightforward to retrospectively date (e.g., hospitalization date), CHR remissions do not similarly come to the attention of the research team outside of scheduled assessments. Accordingly, time-to-remission analyses require assessment of clinical status at more frequent intervals than is typical in longitudinal CHR studies. Moreover, while conversion to psychosis typically ends a CHR individual's clinical tracking, transition to a remitted state does not preclude subsequent recurrence of the CHR syndrome. Therefore, ongoing clinical follow-up is needed after CHR remission to confirm its durability.

It is important to note that analyses of time-to-remission using statistical methods like Cox Proportional Hazard Models must account for both the CHR individuals who convert to psychosis and those who drop out of the study prematurely. A common statistical error in these situations is to binarize the data focused on one outcome at a time, with censoring applied in a similar fashion to participants who are lost to follow-up and participants who develop the competing outcome. More appropriate proportional hazard models have been developed to estimate hazard or survival functions in groups where time to competing clinical outcomes are tracked and distinguished from study discontinuation (93,94).

Heterogeneity of non-remitter (and non-converter) groups with respect to future outcomes

To date, most studies attempting to identify predictors of CHR remission have tended to treat remission as a binary clinical outcome, comparing remitters with non-remitters, and have included among the non-remitters those CHR individuals who progressed to full psychosis. Indeed, both MMN studies described above (56,58) included converters in the non-remitter group, while the P300 studies either excluded converters from their analysis (84) or considered converters separately from non-remitters with a persistent CHR syndrome (25,82). The dichotomization of remission outcomes creates the potential for predictors of remission to be confounded by prediction of conversion effects. The result is that analyses aimed at identifying measures that predict remission are not independent of the prediction of conversion afforded by these same measures, leading to the potentially spurious observation that the same variable that predicts conversion to psychosis based on values from one tail of the variable's distribution also predicts CHR remission based on values from the opposite tail of the distribution. While this can reflect the true state of nature with respect to a biomarker's predictive relationships with CHR outcomes, the degree to which the confounding influence of conversion effects can contaminate and inflate estimates of a variable's accuracy in predicting remission cannot be disentangled unless CHR converters are excluded from the CHR non-remitter group, leaving CHR individuals with a persistent CHR syndrome (CHR-Persistent) as the group to be distinguished from future CHR remitters.

We illustrate this point with a simulation based on features from our prior study showing auditory P300 to predict CHR remission distinct from its prediction of conversion (25). The simulation proceeded by generating 1000 normally distributed samples of 500 CHR individuals with a mean equal to the mean target P300 amplitude z-score value (standardized with respect to the HC mean) from our prior study of $z = -.35$ (25), and a standard deviation of 1 (a simplifying assumption). For each of the 1000 samples, three subgroups were randomly drawn with sizes matched exactly to the CHR-Remitter ($n=90$), CHR-Persistent ($n=135$), and CHR-Converter ($n=73$) subgroups analyzed in Hamilton et al. (25). Our simulation involved a hypothetical scenario in which the baseline biomarker (e.g., P300 z-score) does not actually differ between the CHR-Remitter and CHR-Persistent subgroups but shows a significant ability to predict future CHR-Converter status. In order to demonstrate how this conversion effect alone can drive a spurious prediction of a remission effect when remission is defined by the CHR-Remitter versus CHR-Non-remitter comparison, we systematically varied the strength of the prediction of conversion effect. This was done by drawing the CHR-Converter subgroup from the bottom 85%, 65%, 45%, and 30% of the normally distributed CHR simulation samples, each time without replacement, reflecting progressively larger CHR-Converter versus CHR-Non-converter effect sizes. Because the CHR-Remitter and CHR-Persistent subgroups do not differ, each of these groups was drawn randomly without replacement from the full CHR $n=500$ samples. The set of three subgroups was drawn once from each of 1000 randomly generated full CHR samples, and mean estimates over these 1000 samples were obtained for each subgroup's mean and standard deviation. Figure 1 shows these hypothetical subgroup means and standard deviations, illustrating the lack of difference between the CHR-Remitter and CHR-Persistent subgroups and the progressively greater deficits in the CHR-Converter subgroup. Based on

the same data, Figure 1 also shows the collapse of CHR-Persistent and CHR-Converter groups into a single CHR-Non-remitter subgroup, demonstrating the progressively greater CHR-Remitter versus CHR-Non-remitter effect size that is driven entirely by the increasing deficit in the CHR-Converters. That is, the biomarker appears to increasingly predict CHR remission despite its complete insensitivity to remission when defined by comparison of the CHR-Remitter and CHR-Persistent subgroups. Based on the same simulation approach, but with generation of subgroups across a finer-grained range of CHR-Converter versus CHR-Non-converter effect sizes, Figure 2 shows the number of significant independent group t-tests when testing pairwise subgroup differences for each of the 1000 randomly drawn sets of three subgroups. As can be seen, the CHR-Remitter versus CHR-Non-remitter comparison yields an increasing number of significant t-tests as a function of sampling CHR-Converters from increasingly extreme sections of the leftward tail of the parent CHR sample distribution. Figure 2 also shows the same results expressed as Cohen's d effect sizes, illustrating how the CHR-Remitter versus CHR-Non-remitter effect size grows solely as a function of the increasing CHR-Converter versus CHR-Non-converter effect size.

The above simulation highlights the importance of comparing CHR-Remitters to CHR with a persistent CHR syndrome when attempting to identify variables that predict remission independently of the variable's ability to predict psychosis conversion. One implication of this is that similar concerns and potential confounds arise when predictors of psychosis conversion are derived from comparisons of CHR-Converters with CHR-Non-converters. To the extent that the CHR-Non-converter group includes a subgroup of individuals who subsequently achieve clinical remission, a variable's ability to predict remission can contaminate and inflate the variable's apparent effect size for predicting conversion. As most prior studies predicting conversion in CHR individuals have dichotomized the conversion outcome without regard to the presence of remitters in the non-converter group, this is not just a theoretical concern. In our previous report from the NAPLS2 sample, we initially reported that baseline auditory P3b amplitude was significantly reduced in CHR-Converters relative to CHR-Non-converters with a Cohen's d of 0.26 (25). Most biomarker studies predicting CHR conversion do not further classify CHR-Non-converters into CHR-Remitters and CHR-Persistent subgroups, but when we implemented this additional classification in our previous report, two findings emerged. First, intact target P3b amplitude at baseline significantly differentiated future CHR-Remitters from the CHR-Persistent subgroup, a true prediction of remission effect. Second, the significant CHR-Converter versus CHR-Non-converter effect we reported ($d=0.26$, $p=.048$), when re-defined as a comparison of the CHR-Converter and CHR-Persistent subgroups, was reduced in magnitude ($d=.02$) and was no longer statistically significant ($p=.55$). These data showed that the apparent ability of target P3b amplitude deficits to predict future conversion to psychosis was substantially inflated by a stronger, yet initially obscured, prediction of future CHR remission by intact P3b amplitude at baseline.

Conclusions

While our review documents early evidence that intact MMN and P300 may have clinical utility as predictors of remission from the CHR syndrome, this work is part of a broader and growing literature identifying predictors of CHR remission, including 1) intact cortical

surface area assessed with structural MRI (95–97) (see (98) in current issue), 2) intact cognitive function (99), and 3) clinical trajectories showing symptom and functional improvements (100,101). Thus, there is some convergence across measurement domains showing more intact or neurotypical assessments to predict remission. Attempts to combine clinical, neurocognitive, and biomarker measures, including ERP measures, to predict CHR conversion outcomes have been limited (e.g., 102,103), and no published studies to date have attempted to apply such a multivariate approach to the prediction of CHR remission. Moreover, whether ERP and other biomarkers may not only serve as prognostic predictors of outcomes but also moderate the influence of other factors (e.g., stress, other protective factors) that contribute to CHR outcomes has not yet been studied.

Irrespective of the predictor considered in studies aimed at predicting CHR remission, several general methodological concerns arise that lead us to propose recommendations for future work. Specifically, future CHR research should:

1. Distinguish CHR-Remitter from both CHR-Persistent and CHR-Converter groups in analyses predicting remission, and, conversely, distinguish CHR-Converter from both CHR-Persistent and CHR-Remitter groups when predicting conversion. To estimate relatively uncontaminated remission and conversion effects, each should be calculated with reference to the CHR-Persistent group.
2. Increase the frequency of longitudinal clinical assessments in order to prospectively detect CHR remission and time-to-remission in a manner that approaches the temporal precision with which time-to-conversion is typically assessed.
3. Simultaneously consider conversion and remission outcomes in the same statistical models and include both as competing outcomes in time-to-conversion models.
4. Report metrics regarding the accuracy of individual prediction (e.g., area under the receiver operating characteristic curve) of CHR remission and conversion to extend findings beyond group mean effects, setting the stage for evaluating the potential role of predictors in guiding prognosis and treatment in individual patients.
5. Establish consensus definitions of CHR remission for the field.
6. Standardize optimized biomarker assessments and preprocessing protocols to render results more comparable across studies.

While prediction and prevention of psychosis conversion remains the primary focus of most CHR research, broadening the focus to include CHR remission and other clinical outcomes (e.g., social/occupational functioning) will likely yield novel insights that distinctly inform clinical practice. From a clinical perspective, biomarkers that successfully predict future CHR remission would have utility for assessing prognosis and staged treatment planning, possibly involving intermittent clinical monitoring of those likely to remit while reserving more time intensive (e.g., weekly psychotherapy) and invasive (e.g., psychotropic medication) intervention for those CHR at greatest risk of conversion to full psychosis.

Furthermore, relative to conversion, CHR remission may provide a more feasible and meaningful primary endpoint in clinical trials aiming to develop novel treatments for the CHR syndrome. ERPs are one of many biomarker domains that warrant further study in current efforts to more accurately forecast CHR remission.

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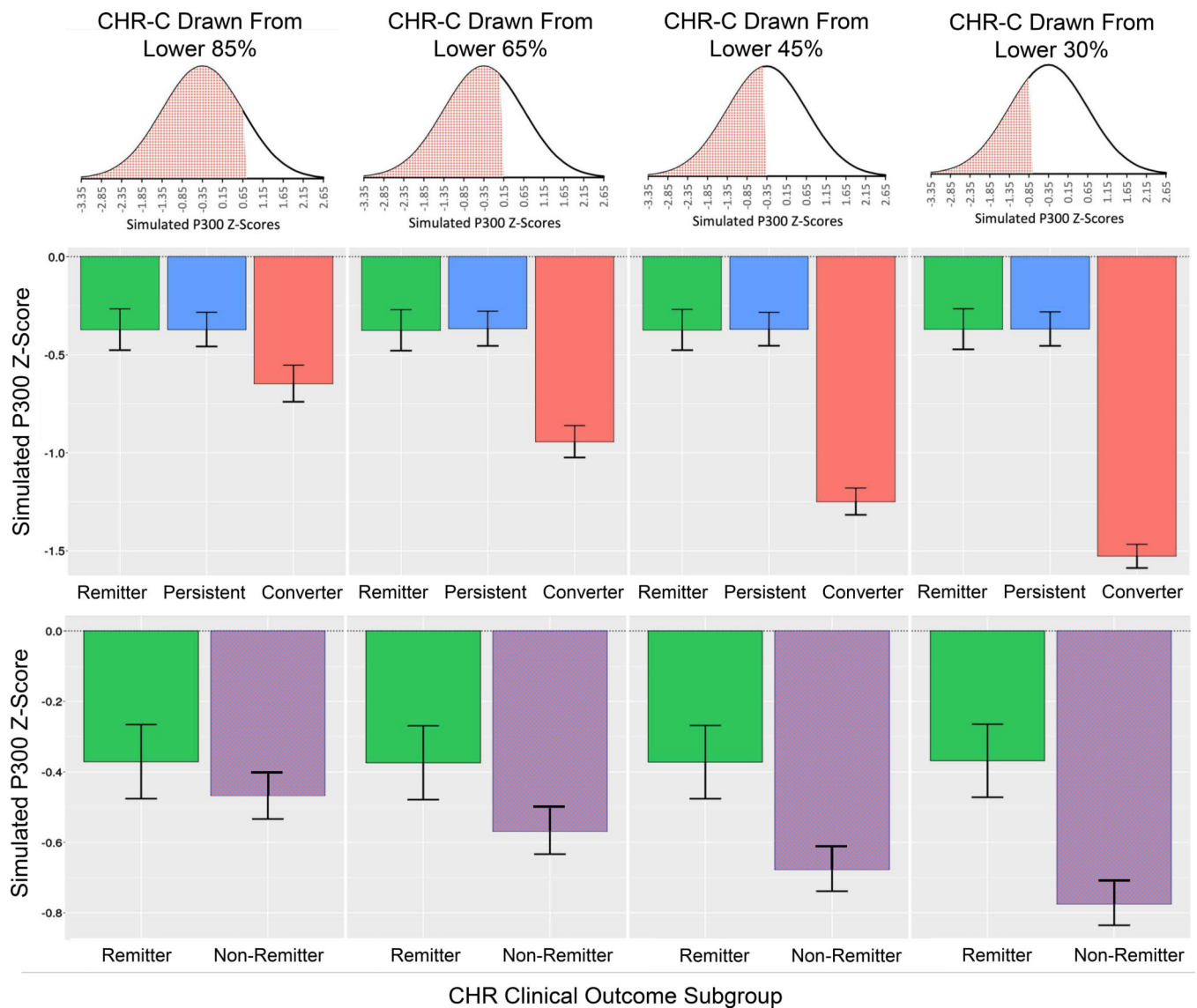


Figure 1. Simulated Clinical High Risk P300 Z-score Data Across Clinical Outcome Sub-Groups.

Simulated data presented here involve a hypothetical scenario in which the baseline biomarker (e.g., P300 z-score) does not differ between CHR-Remitter and CHR-Persistent subgroups but can predict future CHR-Converter status. Plots in the top row show hypothetical subgroup means and standard deviations when the CHR-Converter subgroup is drawn from the bottom 85%, 65%, 45%, and 30% of the normally distributed CHR simulation samples. Plots in the bottom row collapse the CHR-Persistent and CHR-Converter groups into a single CHR-Non-remitter group, showing that the progressively greater CHR-Remitter versus CHR-Non-remitter effect size is driven entirely by the increasing biomarker deficit in the CHR-Converters.

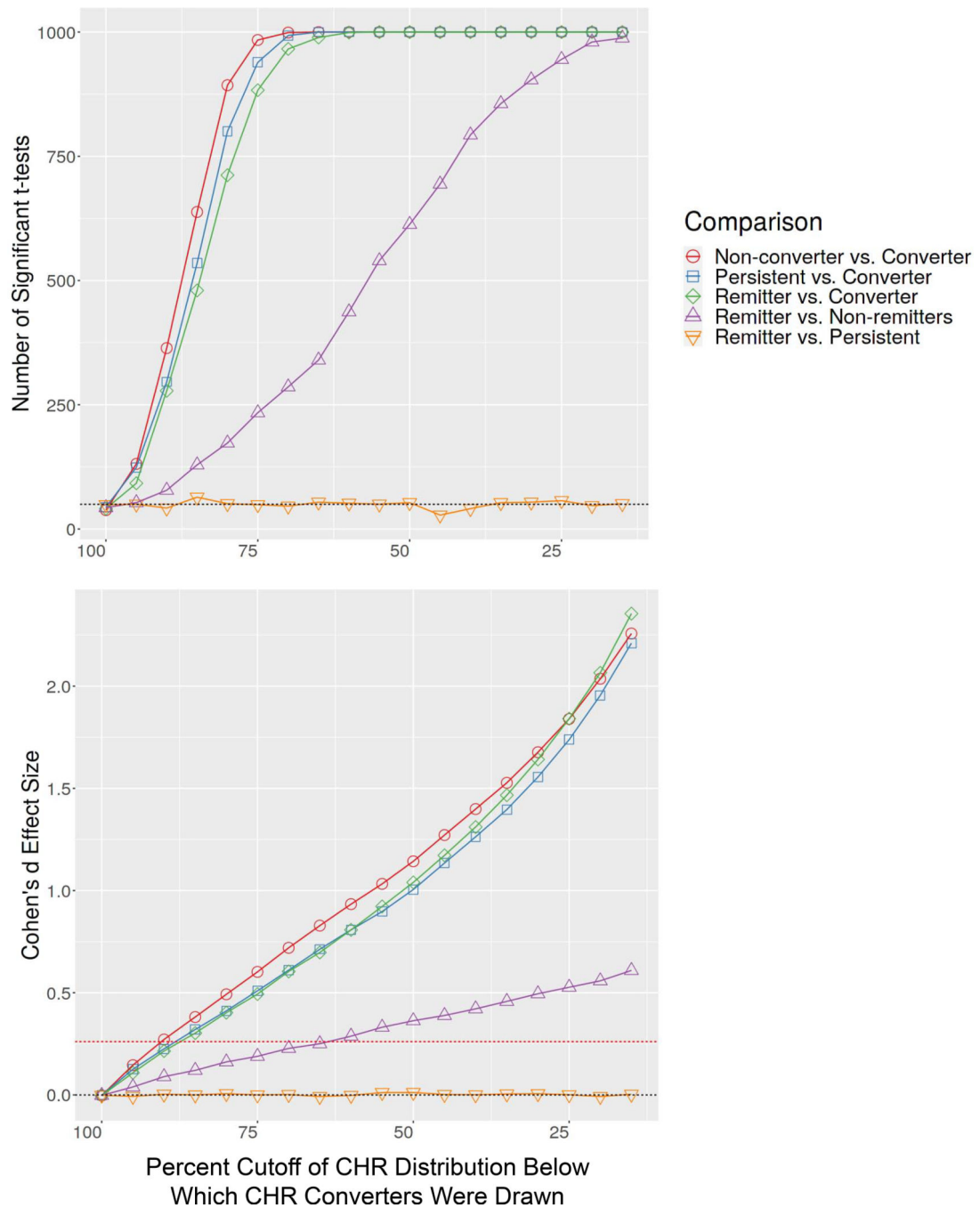


Figure 2. Significant t-tests and Effect Sizes of Simulated Clinical High Risk P300 Z-score Data. The plot on the top shows the number of significant independent samples t-tests when testing pairwise subgroup differences for each of the randomly drawn sets of three subgroups. The CHR-Remitter versus CHR-Non-remitter comparison yields an increasing number of significant t-tests as a function of sampling CHR-Converters from increasingly extreme sections of the leftward tail of the parent CHR sample distribution. The plot on the bottom expresses these results as Cohen's d effect sizes, illustrating how the CHR-Remitter versus CHR-Non-remitter effect size rises as a function the increasing CHR-Converter

versus CHR-Non-Converter effect size. The dotted red line indicates the CHR-Converter vs. CHR-Non-Converter effect size observed for auditory target P300 amplitude z-scores in our prior report (25).

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