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Author(s): Elvira Bramona, , Madiha Shaikha, Matthew Broomea, Julia Lappina, Daniel Bergéb, Fern Daya, James Woolleya, Paul Tabrahama, Mercè Madrec, Louise Johnsa, Oliver Howesa, Lucia Valmaggiaa, Víctor Pérezc, Pak Shamd, Robin M. Murraya and Philip McGuirea
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Corresponding Author's Institution: Institute of Psychiatry, London, UK.

First Author: elvira Bramon, M.D., PhD

Order of Authors: elvira Bramon, M.D., PhD; Madiha Shaikh, BSc Psychology; Matthew Broome, BSc, MBChB, MRCPsych; Julia Lappin, MBBS, MRCPsych; Daniel Berge, MD; Fern Day, BSc; James Woolley, BSc, MBBS, MRCP, MRCPsych; Paul Tabraham, BSc, DCLinPsy; Merce Madre, MD; Louise Johns, MA, DPhil, DCLinPsy; Lucia Valmaggia, MSc, PhD; Victor Perez, MD, PhD; Pak Sham, MBBS, MRCPsych, PhD; Robin Murray, MD, DSc; Philip McGuire, MBBS, MRCPsych, MD, PhD

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Abstract: Background: Individuals with an "At Risk Mental State" (or "prodromal" symptoms) have a 20-40% chance of developing psychosis; however it is difficult to predict which of them will become ill on the basis of their clinical symptoms alone. We examined whether neurophysiological markers could help to identify those who are particularly vulnerable.

Method: 35 cases meeting PACE criteria for the At Risk Mental State (ARMS) and 57 controls performed an auditory oddball task whilst their electroencephalogram was recorded. The latency and amplitude of the P300 and N100 waves were compared between groups using linear regression.

Results: The P300 amplitude was significantly reduced in the ARMS group [8.6 \pm 6.4 microvolt] compared to controls [12.7 \pm 5.8 microvolt] ($p < 0.01$). There were no group differences in P300 latency or in the amplitude and latency of the N100. Of the at-risk subjects that were followed up, seven (21%) developed psychosis.

Conclusion: Reduction in the amplitude of the P300 is associated with an increased vulnerability to psychosis. Neurophysiological and other biological markers may be of use to predict clinical outcomes in populations at high risk.

Dr. Elvira Bramon
Institute of Psychiatry, KCL
(PO Box 63)
De Crespigny Park
London SE5 8AF
United Kingdom
Tel: +44 (0) 20 7848 5036
Email: elivra.bramon@iop.kcl.ac.uk

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Dear editor

Revised manuscript NIMG-07-745

Please find attached a fully revised manuscript titled “Abnormal P300 in people with high risk of developing psychosis”. We also enclose a letter with the comments from the reviewers and our detailed answers on how we have done all the changes requested.

My coauthors and I would be grateful if you could consider this new version for publishing in Neuroimage.

Your Sincerely

Elvira Bramon MD, PhD
Corresponding author

RESPONSE TO REVIEWS - Ms. No.: NIMG-07-745

Title: Abnormal P300 in people with high risk of developing psychosis Corresponding Author: dr Elvira Bramon

Authors: Madiha Shaikh, BSc Psychology; Matthew Broome, BSc, MBChB, MRCPsych; Julia Lappin, MBBS, MRCPsych; Daniel Berge, MD; Fern Day, BSc; James Woolley, BSc, MBBS, MRCP, MRCPsych; Paul Tabraham, BSc, DClinPsy; Merce Madre, MD; Louise Johns, MA, DPhil, DClinPsy; Lucia Valmaggia, MSc, PhD; Victor Perez, MD, PhD; Pak Sham, MBBS, MRCPsych, PhD; Robin Murray, MD, DSc; Philip McGuire, MBBS, MRCPsych, MD, PhD

RESPONSE TO REVIEWER #1:

Thank you for your comments, which have improved the paper and are very encouraging for us. Below are your suggestions in blue italic and how we have amended the manuscript accordingly in black.

This study investigated the differences in P300 between at-risk individuals for psychosis and a matched control group. Reduced P300 amplitude was found associated with at risk state, independent of other demographic variables. The manuscript is well written, is based on standard ERP techniques and the results are clearly presented.

As a minor suggestion, I would request the authors include the criteria of Yung et al. as the journal is not widely available.

These criteria have now been briefly mentioned in the paper. See 1st paragraph of methods section page 4.

Please state if those individuals who progressed to psychosis during follow-up did differ from the others in demographic and ERP variables. Even though preliminary at this stage, this would be of considerable interest!

Compared to the rest of cases at risk, the seven individuals who went on to develop psychosis did not differ significantly in sex or ethnicity (Pearson chi-square $p=0.49$ and $p=0.76$ respectively) or age (t-test; $p=0.93$). Those making a transition to psychosis were marginally more educated but this was only at trend level with a 3 year average difference in the age at which they completed their studies (t-test; $p=0.07$).

Similarly, logistic regression analyses showed that compared to those who remained at risk, the seven cases who made a transition to psychosis had no significant differences in P300 amplitude/latency or N100 amplitude/latency (p values ranging from 0.30 to 0.63 for all four analyses). We have reported these comparisons very concisely and cautiously because referee #2 said that these analyses with only 7 individual making a transition were preliminary and power is limited. Please see results section paragraph 2.

RESPONSE TO REVIEWER #2:

Thank you for your suggestions, which have improved the paper. Below are your comments in blue-italics and how we have amended the manuscript accordingly in black with cross-references to the revised manuscript.

This paper addresses an important and timely topic, namely, whether auditory P300 is reduced in subjects with at risk mental states and whether the P300 predicts subsequent conversion to psychosis. The study finds a significant deficit in P300 in ARMS subjects, relative to controls, replicating a previously published report. The study had the potential to incrementally

contribute to the literature by examining the utility of baseline P300 deficits as a predictor of subsequent conversion to psychosis; however, the negative finding coupled with the lack of power for this analysis (only 7 converters) make this aspect of the study inconclusive. More detailed comments are provided below:

We have added a paragraph in the discussion to acknowledge the limitation of our small group of converters and how we have low statistical power to compare them against those remaining at risk. This is also mentioned in the conclusion.

Please note that referee #1 requested we do undertake a preliminary comparison of converters versus non-converters in demographics as well as P300 and N100. We reported this in the results section very concisely (paragraph 2); although we acknowledge this is inconclusive (discussion paragraph 6 dealing with study limitations).

1. The introduction fails to distinguish P300 elicited by task-relevant target stimuli, sometimes referred to as "P3b", from P300 elicited by task-irrelevant infrequent novel or salient stimuli, sometimes referred to as "P3a". The current study only examines the auditory target P3b, a subset of possible P300 measures that one might choose to study in At-Risk Mental State subjects. It is important to make these distinctions in order for readers unacquainted with the P300 literature to understand the nature of this ERP component and the limits of the generalizability of the current study.

We have now made the distinction between the two P300 sub-components and their nature very clear both in the introduction (paragraph 1 and briefly in paragraph 2) and also in the discussion (paragraph 4).

2. This study lacks a schizophrenia comparison group, making it difficult to place the deficit observed in the ARMS group into perspective within the illness course of schizophrenia. In other words, the current study design does not allow any statements about whether the P300 deficits observed are similar or attenuated relative to schizophrenia patients at their first episode of illness. This design limitation does not invalidate the results, but it does limit the ability to make inferences regarding P300 as trait marker of illness vulnerability versus a pathophysiological marker of illness progression during transition to psychosis. This limitation should be mentioned in the discussion.

We acknowledge this limitation in our study. A direct comparison of controls, high-risk and first episode patients would have been ideal. We included an additional paragraph in the discussion to report this and other limitations (paragraph 6 in discussion).

We published a meta-analysis of patients with schizophrenia (Bramon et al., 2004b) and of unaffected relatives (Bramon et al., 2005). These were the pooled standardized effect sizes (PSES) obtained:

PSES patients v controls: 0.85 (95% CI: 0.65 to 1.05; $p < 0.001$)

PSES relatives v controls: 0.61 (95% CI: 0.30 to 0.91; $p < 0.001$).

PSES calculated above as Cohen's d (Cohen, 1969) allow a direct comparison of the strength of an effect. In this present study the standardized difference between at-risk subjects and controls at centro-parietal sites (averaging CZ and PZ measures as in the meta-analysis) is 0.49. This would indicate that the deficits found in cases at-risk due to prodromal symptoms are less severe than those reported for chronic patients but fall within the confidence interval of the deficits described in

populations with genetic risk, such as the unaffected first degree relatives of patients. We thought it would improve the paper to mention this briefly in the discussion.

3. The EEG/ERP methods are inadequately described. Although we are told that the data were epoched and baseline corrected, we are not told the length of the epochs nor the length of the baseline period subtracted from the epochs. The authors mention that they applied the Neuroscan's ocular correction algorithm, but they do not mention whether epochs were rejected when they contained a voltage value exceeding some criterion (a step that is commonly referred to as "artifact rejection"). Were the EEG epoch data subject to artifact rejection? If so, this should be explicitly described.

We intended to write a brief report and refer readers to our previous papers for further details. However, as requested, we have now amended the manuscript to have a complete EEG methodology section.

Neuroscan have an artifact rejection procedure where epochs containing a voltage value above a chosen value are automatically excluded; however this can lead to substantial data loss. Also, if a group systematically blinks more (as may happen in patients on antipsychotic and other medication) this could lead to bias. We therefore use another ocular artifact rejection procedure, also available in Neuroscan, where the effect of blinks is minimized by linear regression methods and all epochs collected can be used. A template of blinks is obtained for each individual (and each experiment they did) and this is used to obtain coefficients and apply corrections to all other channels. This is a well-known procedure developed by Semlitsch (Semlitsch et al., 1986) and that we have used in several of our previous papers successfully (Bramon et al., 2004a; Bramon et al., 2006; Bramon et al., 2005; Hall et al., 2007a; Hall et al., 2007b; Hall et al., 2006a; Hall et al., 2006b; Hall et al., 2004; Schulze et al., In press).

4. The authors state that the EEG signal was digitized at 500 Hz with a bandpass filter of .05 to 200 Hz. Although the Nyquist rule stipulates that signals need to be sampled at least twice as fast as the highest frequency of interest in order to avoid aliasing, Neuroscan Synamps amplifiers usually implement a more stringent rule, requiring a sampling rate of 4 times the highest frequency of interest as defined by the low pass filter setting. Did the authors use Neuroscan amplifiers? If so, they should confirm that they were able to digitize the EEG signal at 500 Hz with a 200 Hz low pass filter setting. At least using older Synamps amplifiers, this would not have been possible.

Many thanks for spotting this. The sampling rate used in this sample was 1000 Hz. This is now corrected in the methods. We used a Neuroscan Synamps amplifier purchased in 2003 and as you suggest this uses a more stringent Nyquist rule.

5. It is not clear why the authors only examined the N100 to the standard stimulus. The N1 to standards can be rather attenuated due to the lack of sufficient time between auditory stimulus presentations to allow full recovery of the N100 neural generators. The N100 to the target stimuli do not suffer from this recovery constraint because they are well separated in time. Moreover, N100 can be augmented by attention, further motivating an analysis of the N100 elicited by the auditory target stimuli. Addition of this analysis would strengthen the paper.

We reported the N100 to standard stimuli because with 320 of them we get a better signal to noise ratio. We have now added the analyses of N100 response to rare tones (see results section) and we have amended the methods section accordingly. As for the frequent tones, there were no significant differences in N100 to the rare tones between cases at risk and controls. Thus the main findings of the paper remain the same. Because we have had to go back to the original waveforms

and do further signal processing and statistical analyses it has taken us some time to get back with the amended manuscript.

6. An exclusion criterion for the healthy controls, but not the at risk patients, was alcohol or drug abuse or dependence in the past 12 months. This introduced a confound in the group comparison, since the at risk subjects used illicit drugs significantly more than the healthy controls. How can the authors be sure that the group differences they observed are due to the at-risk mental state rather than their increased rate of drug use? Moreover, inclusion of drug use history as a covariate in the model is problematic when the groups differ on the covariate (See Miller and Chapman, 2001, "Misunderstanding analysis of covariance", J of Abnormal Psychology). A better strategy would have been to match the groups on drug use.

The exclusion criteria were misreported in the original manuscript and we have amended the methods section to fully clarify that: (i) A DSM-IV diagnosis of alcohol or drug abuse or dependence was an exclusion criterion for all participants and while the patients were referred to a specialist addictions service controls were simply screened out. (ii) However, recreational substance use (alcohol or illicit drugs) not reaching DSM-IV criteria for dependence/abuse were not an exclusion criteria and that's again for all participants. The reason for this was to avoid recruiting a sample of "super-healthy" participants that could not be generalized to the population we are studying (young inner-city London dwellers where recreational drug usage is very prevalent). Despite using the same inclusion/exclusion criteria in the end our groups were not well matched for recreational drug usage and the cases were significantly more likely to report having recreational use than the controls. It is also important to remember that drug usage for this study relied only on self-report and this has important limitations (compared to urine drug screening). In addition, drug usage could well be regarded as a mediating factor rather than a confounder. In any case, we accept this criticism and, since our data collection is ongoing, we will endeavor to improve the group matching for drug use in future.

As you requested and based on Miller and Chapman 2001, we have re-analysed the study without including the drug effect variables and the paper is now amended to report these final statistics. The findings of the paper have not changed. We have also addressed the issue of drugs in the discussion. Finally, we'd like to highlight that confound from prescribed medication is a much more serious problem in this type of case control research and our sample was un-medicated and mostly naïve to psychotropics.

Due to the lack of matching in recreational drug usage, we have run additional analyses examining a **group X drug use interaction** as well as a **main effect of drugs** in all the paradigms studied and no significant interaction or main effects were found. The estimated differences varied slightly but the findings of the study were unchanged (there still was a significant effect of group (case/control) on P300 amplitude but not on P300 latency, N100 amplitude or N100 latency). All of this indicates that the findings in this study (most of them negative actually) are not confounded by recreational drug usage. Please see all the analyses in an appendix at the end of this letter.

7. In light of the fact that data were collected from a 64 channel scalp montage, it was disappointing that only midline electrodes Fz, Cz, and Pz were analyzed. Moreover, the analysis approach was rather unconventional, apparently treating these three electrodes as a vector of correlated dependent measures. It is more common, and probably more useful, to include electrodes from sites across the scalp in the analysis, and to explicitly include scalp topography factors in the analysis model. This would allow the authors to examine whether the groups showed differences in the scalp topographies of their P300 (or N100) amplitudes and/or latencies.

This is particularly important because a number of prior studies have suggested that P300 shows a left-lateralized deficit over temporal scalp sites in schizophrenia patients, a finding that has been linked to MRI volume deficits of the left superior temporal gyrus in these patients.

As requested we have now examined temporal channels for the P300 wave. We have added a paragraph in the results section to report topographic changes both in P300 and N100 in our study (last paragraph) and in the discussion we also address the issue of lateralization of the P300 deficits (3rd paragraph).

Most of the P300/N100 literature treats FZ, CZ and PZ as independent measures and report at these three locations only. Our statistics colleagues advised analyzing the data in one model, where we take into account that neighboring electrode measures are not really independent but rather have strong correlations (with coefficients between 0.7 and 0.9). We have published similar analyses already in Bramon et al, 2005; Bramon et al, 2006; Schulze et al, 2007.

We agree that the analysis you suggest using electrodes across the scalp including full head topography factors is ideal. However, having collected 64 channels it is extremely complex to execute and to interpret. Other referees may have criticized us given that our sample is of modest size (almost as many electrodes as participants). Thus, given the size of our prodromal sample, we have focused on midline and temporal areas in this paper. We are working to develop the type of analysis you suggest and hope to apply it to our larger datasets.

8. Age was apparently used a covariate in their statistical mode of P300 and N100 effects. It is not clear whether age x group interactions were included or ruled out in their analysis model. The question is whether age relationships with P300 amplitude or latency showed different slopes in the two subject groups, and whether homogeneity of slopes was an implicit assumption of their model. This needs to be clarified.

All our analyses looking at the effect of group on ERPs were adjusted by age as a covariate. This is because several studies and in particular a meta-analysis have found that there is an effect of ageing on P300 especially on its latency which tends to increase in older ages (Polich, 1996). We thought it would be reasonable to adjust our N100 by age too.

We also examined group x age interactions systematically, which were not significant for any of the paradigms examined. In addition the age range of our sample is very narrow (16-35 years) and the two groups did not have significant age differences.

We have amended the final methods section to clarify how we looked at covariates and at interactions. We've also amended the last paragraph of the results section so that this issue of the demographic comparisons is clearer.

9. We are told in the results that there were no significant performance differences between the groups in the oddball task. This conclusion is limited to the accuracy data. Were there reaction time differences between the groups?

The data on reaction time has now been added. Independent sample t-tests indicate that, compared to controls, people at risk for psychosis had similar reaction times. These findings have been briefly added to the results (end of 1st paragraph) and the discussion (4th paragraph). This has required going back to our original files and has taken some time for processing.

12. *In the results, the authors state: "We found a significant effect of group on P300 amplitude, with lower amplitudes in cases at risk than in controls (Coef.= -3.4 microvolt; 95%CI: -5.7 to -1.1; p<0.01)." What is this coefficient? How is it interpreted? Is this the predicted or estimated group effect?*

Please note your comments jump from point 9 to 12. We have not received anything else from the journal. The interpretation of this linear regression un-standardized coefficient is that as you move from controls to at risk cases there is a reduction (negative coefficient) of 3.4 microvolt. This is an estimated effect with a 95% CI -5.7 to -1.1, which is significant. We have amended the results section so that this is clearer and rather than using the term "coefficient" we now call this "Estimated difference". Please note that as we have re-analyzed the whole study to drop the effects of illegal drugs the coefficients for group differences have changed slightly (although the findings of the paper remain unaltered).

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APPENDIX - P300 AMPLITUDE ANALYSES ADJUSTED BY THE MAIN EFFECT OF DRUGS AND BY DRUGxGROUP INTERACTIONS

*GROUP is the main variable of interest
 *DRUGS is the main effect of drugs defined as a dichotomous variable (recreational use of drugs yes or no).
 *GxD is the group by drugs interaction term.

```
. iis id (this accounts for the three observations per participant)

. xi: xtreg p300amp group age sex drugs i.channel gxd, mle
i.channel      _Ichannel_0-2      (naturally coded; _Ichannel_0 omitted)
```

```
Fitting constant-only model:
Iteration 0:   log likelihood = -921.65231
Iteration 1:   log likelihood = -898.56512
Iteration 2:   log likelihood = -893.60016
Iteration 3:   log likelihood = -893.18875
Iteration 4:   log likelihood = -893.18426
```

```
Fitting full model:
Iteration 0:   log likelihood = -811.49141
Iteration 1:   log likelihood = -810.92254
Iteration 2:   log likelihood = -810.90547
Iteration 3:   log likelihood = -810.90546
```

```
Random-effects ML regression      Number of obs      =      276
Group variable (i): id            Number of groups   =       92
```

```
Random effects u_i ~ Gaussian      Obs per group: min =       3
                                      avg =      3.0
                                      max =       3
```

```
LR chi2(7) = 164.56
Log likelihood = -810.90546        Prob > chi2       = 0.0000
```

p300amp	Coef.	Std. Err.	z	P> z	[95% Conf. Interval]
GROUP	-3.133597	1.193447	-2.63	0.009	-5.472711 - .7944828
age	.2347704	.1128663	2.08	0.038	.0135566 .4559843
sex	1.710268	1.03536	1.65	0.099	-.3189993 3.739535

DRUGS		6.442982	4.918535	1.31	0.190	-3.197169	16.08313
Channel CZ		5.510317	.4973753	11.08	0.000	4.535479	6.485155
Channel PZ		7.135006	.4973753	14.35	0.000	6.160168	8.109843
GxD		-5.334248	5.217364	-1.02	0.307	-15.56009	4.891598
_cons		-.0032421	2.879655	-0.00	0.999	-5.647263	5.640779

/sigma_u		4.427319	.3921001			3.721818	5.266553
/sigma_e		3.373364	.1758487			3.045729	3.736243
rho		.6326884	.0500865			.5312293	.7256148

Likelihood-ratio test of sigma_u=0: chibar2(01) = 109.05 Prob>=chibar2 = 0.000

Dropping the GxD interaction term as well as the main effect of DRUGS as these are not significant and as advised by referee we are left with the findings reported in the paper

```
.iis id
. xi: xtreg p300amp group age sex i.channel, mle
i.channel      _Ichannel_0-2      (naturally coded; _Ichannel_0 omitted)
```

```
Fitting constant-only model:
Iteration 0:   log likelihood = -923.94638
Iteration 1:   log likelihood = -899.27156
Iteration 2:   log likelihood = -893.69728
Iteration 3:   log likelihood = -893.19091
Iteration 4:   log likelihood = -893.18426
```

```
Fitting full model:
Iteration 0:   log likelihood = -812.29373
Iteration 1:   log likelihood = -811.95089
Iteration 2:   log likelihood = -811.94539
```

```
Random-effects ML regression      Number of obs      =      276
Group variable (i): id           Number of groups   =       92
```

```
Random effects u_i ~ Gaussian    Obs per group: min =       3
                                avg =      3.0
                                max =       3
```

```
LR chi2(5) = 162.48
Prob > chi2 = 0.0000
Log likelihood = -811.94539
```

p300amp		Coef.	Std. Err.	z	P> z	[95% Conf. Interval]
GROUP		-2.932581	1.066861	-2.75	0.006	-5.02359 - .841573
age		.2406552	.1140261	2.11	0.035	.0171682 .4641422
sex		1.519467	1.038355	1.46	0.143	-.5156714 3.554605
Channel CZ		5.510317	.4973388	11.08	0.000	4.535551 6.485083
Channel PZ		7.135006	.4973388	14.35	0.000	6.160239 8.109772
_cons		.0759236	2.908449	0.03	0.979	-5.624532 5.776379

/sigma_u		4.487321	.3955848			3.775275 5.333666
/sigma_e		3.373364	.1758164			3.045786 3.736173
rho		.6389226	.0495039			.5384387 .7306103

Likelihood-ratio test of $\sigma_u=0$: $\text{chibar2}(01)= 111.70$ $\text{Prob}\geq\text{chibar2} = 0.000$

Abnormal P300 in people with high risk of developing psychosis

Elvira Bramon¹ MD, PhD, Madiha Shaikh¹ BSc, Matthew Broome¹ BSc, MBChB, MRCPsych, Julia Lappin¹ MBBS, MRCPsych, Daniel Bergé² MD, Fern Day¹ BSc, James Woolley¹ BSc, MBBS, MRCP, MRCPsych, Paul Tabraham¹ BSc, DClinPsy, Mercè Madre³, MD, Louise Johns¹ MA, DPhil, DClinPsy, Lucia Valmaggia¹ MSc, PhD, Víctor Pérez³ MD, PhD, Pak Sham⁴ MBBS, MRCPsych, PhD, Robin M. Murray¹ MD, DSc, Philip McGuire¹ MBBS, MRCPsych, MD, PhD.

¹ Institute of Psychiatry, London, UK.

² Hospital del Mar, IAPS, Barcelona, Spain.

³ Hospital de Sant Pau, Barcelona, Spain

⁴ Li Ka Shing Faculty of Medicine, Honk Kong University, China

ADDRESS FOR REPRINTS

Elvira Bramon

Institute of Psychiatry, Division of Psychological Medicine – box 63, De Crespigny Park, London, SE5 8AF, United Kingdom.

Tel: 0207 848 5036

Fax: 0207 701 9044

E-mail: elvira.bramon@iop.kcl.ac.uk

INTRODUCTION

Individuals with an ‘At Risk Mental State’ (ARMS) experience ‘prodromal’ symptoms and previous studies report that between 20 and 40% of them make a transition to psychosis within one or two years (Addington et al., 2007; Broome et al., 2005a; Klosterkötter et al., 2001; McGlashan et al., 2007; McGlashan et al., 2004; Morrison et al., 2002; Olsen and Rosenbaum, 2006; Schultze-Lutter et al., 2007; Yung et al., 2007; Yung et al., 2003; Yung et al., 2004). The basis of the vulnerability to psychosis in this group is unknown and, whilst evidence shows that psychological and pharmacological interventions improve outcomes (Bechdolf et al., 2005; McGorry et al., 2002; Miller et al., 2003; Phillips et al., 2005; Ruhrmann et al., 2005; Woods et al., 2003), treating high risk subjects remains controversial since most of them are not destined to develop the disease (Broome et al., 2005b; Cornblatt et al., 2001; Haroun et al., 2006). The identification of biological measures associated with a subsequent transition to psychosis would help to target early treatment to those who require it (Bender et al., 2007; Bramon et al., 2004a; Eastvold et al., 2007; Mason et al., 2004; Pantelis et al., 2003; Simon et al., 2007; van der Stelt and Belger, 2007).

Neurophysiology provides a non-invasive method to evaluate brain function related to cognitive and perceptual processes *in vivo*. The P300 wave reflects cortical activity during a form of continuous performance task in which subjects respond to target stimuli embedded at random in a sequence of standard stimuli. This event-related potential is more specifically known as the P3b in order to distinguish it from the P3a, a response to task-irrelevant novel infrequent stimuli not examined in this paper (Araki et al., 2006; Frodl-Bauch et al., 1999; Laurens et al., 2005; Mathalon et al., 2000; Salisbury et al., 2004; Salisbury et al., 2001; Sponheim et al., 2006). Another EEG marker investigated here, the N100 wave, reflects the early phase of attentive stimulus processing (Boutros et al., 2004; McCarley et al., 1991).

A meta-analysis of studies over the last decade indicates that the amplitude of the P300 (the P3b wave) is severely reduced and its peak is substantially delayed in patients with schizophrenia (Bramon

et al., 2004b). Qualitatively similar, but less severe, deviances in amplitude and latency are also evident in the non-psychotic relatives of patients with schizophrenia (Blackwood et al., 1991; Bramon et al., 2005; Bramon et al., 2004b; Frangou et al., 1997). P300 deviances may thus constitute markers of a genetic predisposition to develop/transmit psychosis (Ahveninen et al., 2006; Braff et al., 2007; Bramon et al., 2006; Calkins et al., 2007; Cannon and Keller, 2006; Golimbet et al., 2006; Gottesman and Gould, 2003; Hall et al., 2006a; Hall et al., 2006b; Mulert et al., 2006; Price et al., 2006; Schulze et al., In press; Sumich et al., 2006; Sumich et al., 2007; Turetsky et al., 2007). Some, but not all, previous studies show N100 amplitude reductions in schizophrenic patients (Ahveninen et al., 2006; Brown et al., 2002; Frangou et al., 1997; Heinks-Maldonado et al., 2007; Javitt et al., 2000; Kogoj et al., 2005; O'Donnell et al., 2004; Pfefferbaum et al., 1984; Roth et al., 1981; Roth et al., 1980; Shelley et al., 1999; Sumich et al., 2006; Sumich et al., 2007; Winterer et al., 2001) but the N100 wave has not been examined in populations with high risk of developing psychosis.

Van der Stelt et al (van der Stelt et al., 2005) were the first to report P300 amplitude reductions in prodromal cases, which were of similar severity to those found in patients with recent onset as well as chronic schizophrenia. We set out to replicate this finding and to examine other EEG markers such as the N100 wave in an independent sample.

METHODS AND MATERIALS

Subjects were 35 people with an at risk mental state according to criteria established by Yung and colleagues, which include people with sub-clinical “attenuated” psychotic experiences, individuals with psychotic symptoms of insufficient duration to reach a diagnosis (brief limited intermittent psychotic symptoms known as BLIPS), and finally individuals with a schizotypal personality disorder or with a first-degree relative with psychosis who had a significant decline in function (Yung et al., 2005). These were compared against 57 healthy volunteers with no family or personal history of psychotic disorders. At risk subjects were recruited through the clinical service “Out-reach And Support In South London”(OASIS) (Broome et al., 2005a). Controls were recruited from the same geographical area by advertisements in the local press. Participants were excluded if they had

neurological disorders, or head injury with loss of consciousness longer than ten minutes or a DSM-IV diagnosis of alcohol or illegal substance dependence or abuse in the 12 months prior to assessment. Alcohol and other substance use, not reaching criteria for dependence or abuse, did not constitute exclusion criteria to ensure the sample was representative of our population. Of the thirty five cases at risk all but three were antipsychotic naïve and none of them were taking antipsychotics at the time of EEG testing. None of the controls were on any psychotropic medication at the time of EEG testing. All participants gave written informed consent to enter the study. This research was approved by the Ethical Committee at the Institute of Psychiatry.

Clinical assessments: All participants were interviewed to collect information on socio-demographic, physical and mental health data and the timing and nature of any symptoms. The instrument used to identify at risk cases was the Comprehensive Assessment of At-Risk Mental States (CAARMS) (Yung et al., 2005). The Family Interview for Genetic Studies (Nurnberger et al., 1994) was used to obtain/rule out any psychiatric diagnoses in the participant's first and second degree relatives. Transition to psychosis was defined using the threshold criteria in the CAARMS (Yung et al., 2005).

P300 paradigm: The P300 and N100 were obtained with a standard auditory oddball paradigm (Bramon et al., 2005). Stimuli were four hundred 80 dB tones, with a $2 (\pm 0.2)$ seconds inter-stimulus interval presented through bilateral intra-aural earphones. 80% of the tones were 'non-targets' of 1000 Hz and 20% were 'targets' of 1500 Hz in a random sequence. Subjects were instructed to keep their eyes open and press a button in response to target tones only. EEG data were collected from 64 scalp sites according to the 10/20 International System (Jasper, 1958) and were grounded at Fpz using synered electrodes in a cap. Bilateral mastoids served as reference and vertical and horizontal electro-oculographs monitored eye movements. Data were continuously digitised at 1000 Hz with a 0.05 to 100 Hz band-pass filter (24 dB/octave roll-off). Impedances were kept below 5 KOhms. A Neuroscan linear regression procedure was employed to minimise ocular artifacts (Semlitsch et al., 1986). The continuous EEG recording was epoched (-100 to 700 ms), baseline corrected using the pre-stimulus interval (-100 to 0 ms), band-pass filtered 0.05 to 45 Hz and averaged for targets and non-targets

separately (Bramon et al., 2005; Frangou et al., 1997). The P300 was defined as a positive waveform generated by the target tones and peaking between 280-500 ms post-stimulus. The N100 was defined as the first negative wave peaking between 60 and 140 ms. The N100 wave was analysed for both frequent and rare tones (Brown et al., 2002) and the statistical details are reported for the rare tones by default and for frequent tones wherever relevant as stated in the text. P300 and N100 peak amplitudes and latencies were measured using a computer algorithm, which made the process blind to group affiliation.

Statistical analysis: The socio-demographic characteristics and task performance between groups were compared using χ^2 for categorical and t-test for continuous variables. The P300 and the N100 waves were compared between cases at risk and healthy controls using linear mixed models fitted with maximum likelihood methods. FZ, CZ and PZ measures were analysed and the correlations between these electrodes within each individual were accounted for by including random intercepts for participants. This is needed to maintain correct type-1 error rates (for similar two-level or three-level nested models see (Bramon et al., 2006; Bramon et al., 2005). The P300 amplitude was the dependent variable and group (at risk or control), electrode (FZ, CZ, PZ), sex and age were the independent variables. We examined interactions of group by sex, group by age and group by electrode. Similar analyses were conducted with P300 latency, N100 amplitude and N100 latency as dependent variables. For the P300 wave only, an additional analysis tested the group differences comparing left and right temporal electrodes (T7 and T8 respectively) again adjusting by age and sex and relevant interactions. Boxplots were used to examine departures from normality and none were detected. All analyses were conducted in STATA 9.2 using the xtreg and xtlogit commands for regression analysis adjusting for clusters (electrode measures) in the data.

RESULTS

This sample included 35 cases with at risk mental states (ARMS) as defined by Yung and colleagues (Yung et al., 2005) as well as 57 healthy volunteers. As can be seen in table 1, the two participant

groups were similar in demographics including age, sex, ethnicity and education. Subjects with at risk mental states were significantly more likely to report recreational drug use ($p < 0.001$) and also smoked significantly more cigarettes per day ($p < 0.01$). Of the at risk group, 66% suffered attenuated sub-threshold psychotic symptoms, 11% had brief limited intermittent psychotic symptoms (BLIPS), another 3% were included because of having a schizotypal personality or a family history of psychosis in addition to functional decline. Finally, 11% had both attenuated and BLIPS symptoms and 9% fulfilled both attenuated and trait and state criteria.

There were no significant differences between groups in terms of task accuracy or speed. Thus correct responses were $99.0\% \pm 2.0\%$ for controls and $98.9\% \pm 1.9\%$ for the at risk group. Reaction times for the button press were 0.48 ± 0.21 and 0.50 ± 0.16 seconds in controls and at risk people respectively.

Table 1 about here

Two at risk participants disengaged from the service shortly after inclusion and their clinical outcome is unknown. These drop outs belonged to the attenuated symptoms category and did not differ in socio-demographic characteristics from those followed up successfully. Of the remaining 33 participants, after an average follow up of 23.5 months (range 1.6 to 46.8; SD 13.5 months), seven subjects (21.2%) developed a full-blown psychotic episode. Amongst the cases at risk the mean GAF score at the end of the follow up period was 71.1 (range 40 to 90; SD 14.2). Compared to the cases remaining at risk, the seven individuals making a transition to psychosis did not differ significantly in age, sex, ethnicity, education or in their P300 or N100 amplitudes and latencies.

Cross-sectional comparison between "At risk" cases and controls in event related potentials:

We found a significant effect of group on P300 amplitude, with lower amplitudes in cases at risk than in controls (Midline estimated difference = -2.9 microvolt; 95%CI: -5.0 to -0.8 ; $p < 0.01$. Temporal channels Est. Dif. = -1.6 microvolt; 95%CI: -3.1 to -1.0 ; $p = 0.04$). The two groups did not differ significantly in P300 latency, N100 amplitude and N100 latency (both frequent and rare tones were

examined for N100).

Topographic effects:

The P300 amplitude was largest and its latency most delayed at parietal compared to frontal sites (Est. Dif. amplitude PZ-FZ= 7.1 microvolt; 95%CI: 6.2 to 8.1; $p<0.01$. Est. Dif. latency PZ-FZ= 23.7 milliseconds; 95%CI: 14.0 to 33.4; $p<0.01$). The P300 amplitude was larger at left temporal than right temporal electrodes in both cases and controls (T7-T8 Est. Dif.= 0.9 microvolt; 95%CI: 0.03 to 1.8; $p=0.04$). The group by temporal region interaction was not significant suggesting no evidence of lateralisation in the P300 amplitude deficits observed in our at-risk cases. The P300 latency showed no differences between left and right temporal regions. Finally, the N100 amplitude was larger (in absolute value) and its latency greater at frontal than parietal electrodes (Est. Dif. amplitude PZ-FZ= 3.8 microvolt; 95%CI: 3.4 to 4.2; $p<0.01$. Est. Dif. latency PZ-FZ= -13.3 milliseconds; 95%CI: -17.1 to -9.5; $p<0.01$).

Demographic variations:

There were no significant findings for the P300 wave except for ageing, which marginally increased P300 amplitudes (Est. Dif= 0.24 microvolt; 95%CI: 0.02 to 0.46; $p=0.04$). As for the N100 amplitude, in this sample women had a significantly greater amplitude than men (Est. Dif.= -1.2 microvolt; 95%CI: -2.2 to -0.2; $p=0.02$). Men had delayed N100 latencies compared to women (Est. Dif.= -8.1 ms; 95%CI: -13.7 to -2.4; $p<0.01$). Ageing was associated with delayed N100 latency to the frequent tones (Est. Dif.= 0.6 ms; 95%CI: 0.1 to 1.2; $p=0.02$); however, this effect did not reach statistical significance for the N100 to the rare tones. Given the size of our sample and its narrow age range these minor demographic differences need to be taken with caution. Finally, there were no significant interactions of group with age, sex and topography covariates for any of the waves examined. Figures 1 and 2 provide further details about group comparisons in P300 and N100 performance.

Figure 1 about here

Figure 2 about here

DISCUSSION

Our hypothesis, that the P300 in subjects with an at-risk mental state (AMRS) would differ from that in healthy volunteers, was confirmed, with its amplitude significantly reduced in the ARMS group. From twin studies we know that P300 traits are reliable and heritable (Hall et al., 2006a; Hall et al., 2006b; Hall et al., 2004; van Beijsterveldt and van Baal, 2002). P300 amplitude reductions as well as latency delays constitute markers of vulnerability for psychosis, as they are evident in the unaffected relatives of patients (Blackwood et al., 1991; Bramon et al., 2005; Bramon et al., 2004b; Frangou et al., 1997; Pierson et al., 2000; Turetsky et al., 2000; Winterer et al., 2003) and they show a significant genetic correlation with schizophrenia and bipolar disorder (Hall et al., 2007a; Hall et al., 2007b).

As for the topography, the P300 amplitude deficits in the at-risk cases were consistently observed in midline as well as temporal sites (McCarley et al., 1991; McCarley et al., 2002; Morstyn et al., 1983). However, we found no evidence that these deficits were left-lateralized and this could be due to our paradigm involving a button press; which is thought to diminish the abnormal P300 asymmetry in schizophrenia (Ford et al., 1994; Pfefferbaum et al., 1989; Renoult et al., 2007; Salisbury et al., 2001).

While ageing and task difficulty are known to influence P300 performance, especially its latency (Mori et al., 2007; Polich, 1996); demographic confounders are unlikely to explain our findings and all analyses were adjusted for age and sex. Use of cannabis and other drugs is a known risk factor for psychosis (Arseneault et al., 2004) and since the at-risk group reported recreational drug consumption more often than the controls this could have contributed to our findings. However, additional analyses (available from the authors upon request) show that in this sample illicit drug use had no significant main effect on the P300 amplitude or any of the other paradigms examined and that there were no significant group by drug use interactions. Finally, since all but three of the ARMS subjects were naïve to antipsychotic medication, and no subject was on antipsychotics at the time of EEG testing, the reduction in P300 amplitude is unlikely to be confounded by pharmacological treatment (Laurent

et al., 1999). Our findings are consistent with the data from two previous smaller studies of the P300 in the ARMS, both of which reported reductions in amplitude (Mathalon et al., 2004; van der Stelt et al., 2005).

The P300 wave is associated with a task that involves attentional processing and a degree of executive functioning. An abnormal P300 in the ARMS is thus consistent with data from neuropsychological studies of this group, which suggest that the ARMS is associated with impaired performance on tasks that engage attention (such as the CPT) and executive processes (Brewer et al., 2005; Cornblatt et al., 2004; Lencz et al., 2006; Pukrop et al., 2007; Woods et al., 2003). Our findings are also consistent with data from a functional imaging study of the P300 which indicated that subjects with an at-risk mental state showed less activation in the temporal cortex than controls but more than patients with schizophrenia (Morey et al., 2005). Interestingly, whilst the at-risk cases showed normal accuracy and reaction time in the P300 task at a behavioral level, their cortical physiology was impaired. Increasing task difficulty and using multi-modal techniques (Bender et al., 2007; Molina et al., 2007; Price et al., 2006; Sponheim et al., 2006) should increase our ability to detect subtle cognitive changes in the prodrome of psychosis.

Like Van der Stelt et al (van der Stelt et al., 2005) we failed to find latency deficits in the ARMS group. Because individuals at increased genetic risk of schizophrenia consistently show moderate latency delays (Bramon et al., 2005), we expected a similar finding in populations at clinical risk. However, both available studies may lack statistical power and thus P300 latency deficits can not be ruled out until larger samples can be examined. Furthermore, our paradigm as well as Van der Stelt's only allows us to examine the P3b wave (a response elicited by the target stimuli that require a response from the subject). More complex P300 experiments incorporating additional infrequent novel stimuli that generate the P3a response would be worth investigating in the prodrome (Araki et al., 2006; Frodl-Bauch et al., 1999; Laurens et al., 2005; Mathalon et al., 2000; Salisbury et al., 2004; Salisbury et al., 2001; Sponheim et al., 2006; Sumich et al., 2007).

A limitation of this study is that we lacked a sample of patients with schizophrenia to compare with our at-risk and control groups. Similarly, since only seven of our cases at risk converted to psychosis we do not have sufficient statistical power to compare them against those who remained at risk after follow up. Meta-analyses show that, compared to controls, P300 amplitude deficits are moderate-severe in chronic patients with schizophrenia with a pooled standardised effect size calculated as Cohen's d of 0.85 (95% CI: 0.65 to 1.05; $p < 0.001$) and of moderate severity in their unaffected relatives with a pooled standardised effect size of 0.61 (95% CI: 0.30 to 0.91; $p < 0.001$) (Bramon et al., 2005; Bramon et al., 2004b; Cohen, 1969). Pooled standardised effect sizes as calculated above allow a direct comparison of the strength of effects (Cohen, 1969). In this present study the standardized difference between at-risk subjects and controls at centro-parietal sites (averaging CZ and PZ measures as in the meta-analysis) was 0.49. These data suggest that the deficits found in cases at-risk due to prodromal symptoms are less severe than those reported for chronic patients but, since they fall within the confidence interval, are comparable to the deficits described in populations with genetic risk, such as the unaffected first degree relatives of patients. However, direct comparisons, ideally with first episode patients, and especially longitudinal studies are needed to confirm this finding.

As an abnormal P300 is thought to reflect increased genetic risk for schizophrenia, this is compatible with the view that the high risk of psychosis in the ARMS may have a genetic basis. While only a minority of subjects in most ultra-high risk samples, including our own, have a known family history of psychosis, subjects could still be carrying risk alleles of genes that predispose to psychosis. Indeed, the attenuated psychotic symptoms that are characteristic of at-risk mental state populations were also described in approximately 50% of young adults who had a first degree relative with schizophrenia; and those young relatives who had additional high levels of schizotypy had a risk of developing psychosis comparable to the ARMS group (Johnstone et al., 2005). Both the relatives of patients with schizophrenia and individuals with an ARMS show neuropsychological and volumetric MRI abnormalities that are qualitatively similar to those seen in schizophrenia but are quantitatively less severe (Brewer et al., 2005; Woods et al., 2003). To date no studies of genetic factors in the ARMS

have been completed, but these are ongoing and may clarify the contribution of genes to the vulnerability to psychosis in this group (Bender et al., 2007).

Neither the amplitude nor the latency of the N100 wave was abnormal in our ARMS group. Amplitude reductions and latency delays of the N100 wave have been described in chronic schizophrenia (Frangou et al., 1997; Karoumi et al., 2000; O'Donnell et al., 2004; Wood et al., 2006), but have not been evident in the non-psychotic relatives of patients (Frangou et al., 1997; Karoumi et al., 2000). To our knowledge, this is the first examination of N100 performance in the at-risk mental state. The existing evidence, although more limited than that for P300, indicates that the N100 deficits are not markers of risk but rather a correlate of chronic psychotic symptoms (Brown et al., 2002; Javitt et al., 2000; Kogoj et al., 2005; O'Donnell et al., 2004; Roth et al., 1980; Shelley et al., 1999; Sumich et al., 2007).

As for clinical outcomes after an average of two years follow up, the rate of transition in our sample was lower than in early studies of the ARMS, but there is considerable variation across centres, reflecting different populations and ascertainment methods (Addington et al., 2007; Broome et al., 2005a; Klosterkotter et al., 2001; McGlashan et al., 2007; McGlashan et al., 2004; Olsen and Rosenbaum, 2006; Schultze-Lutter et al., 2007; Yung et al., 2007; Yung et al., 2003; Yung et al., 2004), and a rate of 21% is in line with that reported in recent work from comparable populations in the UK (Morrison et al., 2002).

In summary, our data and a previous smaller study (van der Stelt et al., 2005) both indicate that the at-risk mental state is associated with a significant reduction in the amplitude of the P300 wave, possibly reflecting an underlying genetic predisposition. A longitudinal analysis examining whether P300 and other biological markers at baseline can help to predict clinical outcomes would be granted; however, large samples or a meta-analysis will be required to achieve sufficient statistical power.

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FINANCIAL DISCLOSURES

None of the co-authors has any conflict of interests to declare.

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Table 1: Demographics of the sample with at-risk mental states (ARMS) and controls.

ARMS: At-risk mental state. The two groups are well matched for the main demographic potential confounders.

SD: standard deviation.

Figure 1: P300 and N100 amplitude and latency comparisons between at risk cases and controls

Bar chart providing P300 and N100 amplitude / latency (means \pm 1 S.D) by electrode and group.

P300 amplitude: Coef.= -3.4 microvolt; 95%CI: -5.7 to -1.1; $p<0.01$.

P300 latency: Coef.= 1.9 microvolt; 95%CI: -15.8 to -19.6; $p=0.83$.

N100 amplitude: Coef.= -0.1 microvolt; 95%CI: -1.3 to 1.0; $p=0.83$.

N100 latency: Coef.= -2.1 microvolt; 95%CI: -7.5 to 3.4; $p=0.46$.

Figure 2: Group average P300 and N100 waves for 35 cases with at risk mental states and for 57 controls

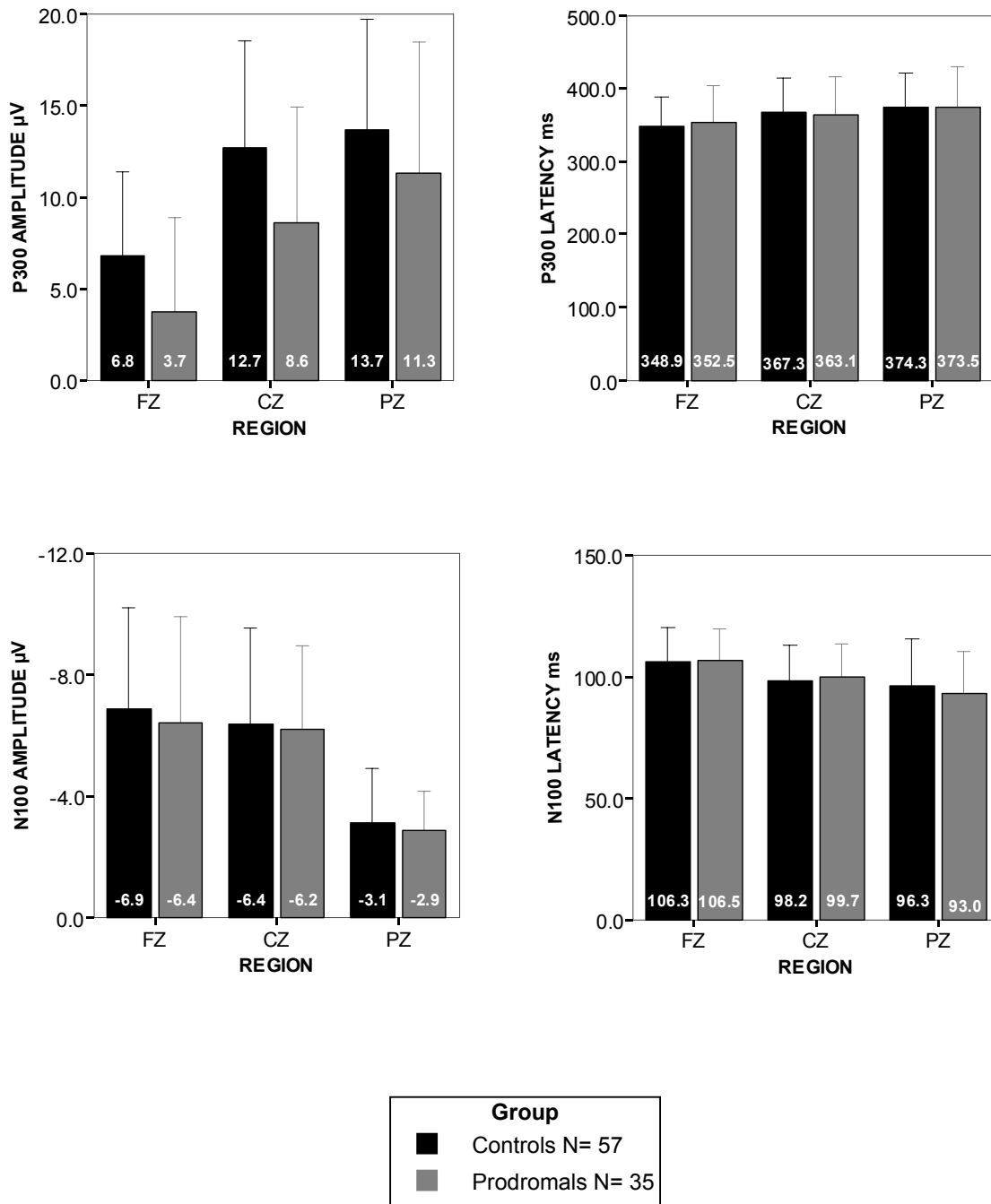
Group averages of P300 and N100 at sites FZ, CZ and PZ. No group differences observed in P300 latency or in the amplitude and latency of the N100. A significant reduction in P300 amplitude was found in the prodromal group.

4. Table 1

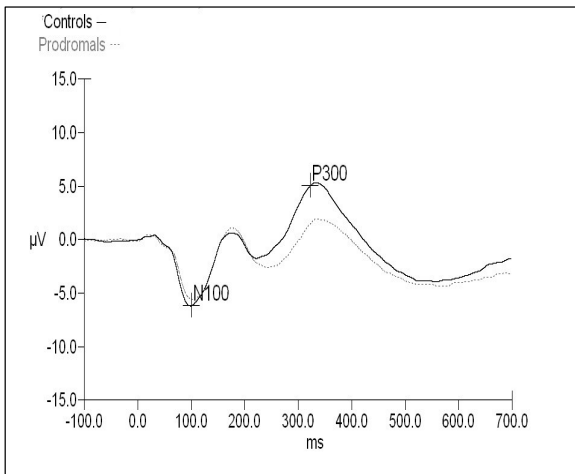
Demographic variables		ARMS	Controls	Group comparisons
		N= 35	N= 57	
Sex	% male	60%	42%	$X^2 (1)= 2.78; P=0.13$
Ethnicity	White	65.7%	73.7%	$X^2 (1)= 1.674; P=0.43$
	Black	28.6%	17.6%	
	Other	5.7%	8.8%	
Age	Years \pm SD	24.57 \pm 4.6	24.53 \pm 4.5	T-test; P=0.96
	range	16 – 35	19 - 35	
Education				
	(age completed studies)	19.37 \pm 3.2	20.60 \pm 3.7	T-test; P=0.10
Regular drug use %		31.4%	1.8%	$X (1); P < 0.001$
Number of cigarettes/day \pmsd		6.09 \pm 7.2	1.55 \pm 4.1	T-test; P<0.01
P300 performance				
	% correct responses	98.9 \pm 1.9 %	99.0 \pm 2.0 %	T-test; P=0.62

5. Figure 1

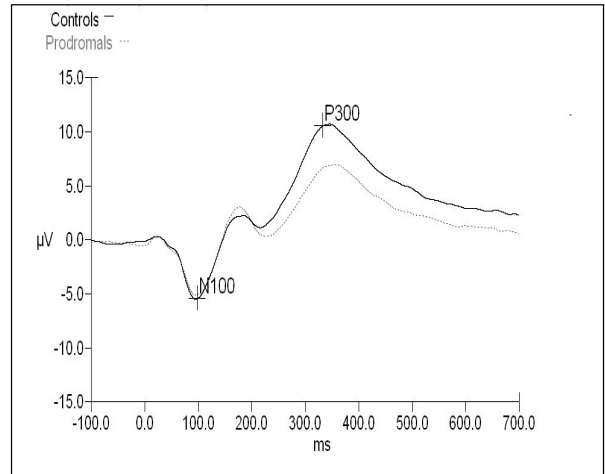
[Click here to download 5. Figure: Figure1_final.pdf](#)



FZ



CZ



PZ

