Hippocampal volume reduction specific for later transition to psychosis or substance-associated effects?

We read with great interest the article by Witthaus and colleagues[1] recently published in the *Journal of Psychiatry and Neuroscience*. The authors found that, compared with controls, patients at ultra-high risk (UHR) had significantly smaller volumes of the hippocampus corpus and tail bilaterally. The UHR patients who later developed psychosis had smaller right hippocampus corpus and tail volumes than did those who did not develop psychosis. The authors concluded that the hippocampal volume reduction may be indicative of the prodromal phase of schizophrenia and may represent a risk factor for transition into psychosis.

However, significantly reduced (right) hippocampal volumes in UHR patients with later transition are in contrast to previous region-of-interest studies. We and others[2,3] showed no volumetric hippocampal differences between converters and nonconverters, suggesting that hippocampal volumes are not related to an at-risk mental state with later transition to psychosis. Instead, there is evidence for hippocampal and parahippocampal volume reductions developing as the disease progresses, at least during the first psychotic episode.[4,5]

These inconsistent results may be attributable to different ascertainment strategies, transition criteria, clinical follow-up periods, cannabis abuse and medication effects.[6] Witthaus and colleagues[1] reported that within 9 months after magnetic resonance imaging, 2 UHR patients made the transition to psychosis, and 6 patients were lost to clinical follow-up and therefore considered to be converters (assumption based on available clinical information). In contrast to our and other previous neuroimaging studies, patients at high risk of psychosis were followed-up for at least 1 year, and standardized criteria[7] were applied to determine if any patients made the transition to psychosis.

In addition, Witthaus and colleagues[1] did not report complete information on the medication status of the UHR patients. They stated that 11 of 29 patients had received atypical antipsychotics, alluding to short-term risperidone or olanzapine treatment. However, it is unclear whether those at UHR who later transitioned to psychosis received more or less antipsychotics compared with UHR patients who did not transition.

This raises the question as to whether the volumetric alterations seen in the UHR group could be an effect of antipsychotic medication. We agree with the authors that the results of the study cannot simply be explained by an effect of antipsychotic medication taken only for an average of 1.9 days. However, 2 recently published systematic reviews on the effects of antipsychotics on the brain concluded that antipsychotics may contribute to brain structural changes observed in psychosis and that their effects are regional rather than global.[8,9]

Moreover, UHR individuals with cannabis abuse were included if their psychotic symptoms began before the onset of cannabis abuse. However, recently published studies have shown an intrinsic influence of cannabis on brain structure and function.[10,11] There is evidence that the degree of acute psychotic symptoms following tetrahydrocannabinol administration modulated mediotemporal function among healthy men.[11] Furthermore, continuous cannabis use over 5 years led to progressive loss of brain volume among first-episode schizophrenia patients.[10]

Therefore, it would have been interesting to perform a statistical analysis covarying for effects of cannabis use or to compare hippocampal volumes in UHR patients with and without cannabis abuse. This could address the putative effect of cannabinoids on the hippocampus.

Despite the fact that neuroimaging studies have provided evidence that, independent of psychotropic substances, there are detectable anatomic abnormalities at the level of total and regional brain volumes, the effects of cannabis and antipsychotics on hippocampal volume remain elusive. Until we have reliable UHR studies addressing the longitudinal effects of psychotropic substances on brain structures as the hippocampus, we must keep the potential impact of substance-associated effects in mind.

Stefan Borgwardt, MD, PhD
Renata Smieskova, MD
Kerstin Bendfeldt, PhD
Eva Bühlmann, MD
Gregor Berger, MD
Jacqueline Aston, MD
Ute Gschwandtner, MD, PhD
Marlon Pflueger, PhD
Rolf-Dieter Stieglitz, PhD
Anita Riecher-Rössler, MD, PhD
Psychiatric Outpatient Department
Psychiatric University Hospital
Ernst-Wilhelm Radue, MD, PhD
Medical Image Analysis Center
University Hospital Basel
Basel, Switzerland

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Hippocampal alterations in ultra-high risk patients are independent from medication and cannabis use

In their comment on our article entitled "Hippocampal subdivision and amygdalar volumes in patients in an at-risk mental state for schizophrenia,"[1] Borgwardt and colleagues raise some critical questions regarding our finding that hippocampal volume loss is related to an at-risk mental state. Instead, they argue that smaller right hippocampus corpus and tail volumes in ultra-high risk patients (UHR) who later developed schizophrenia compared with those who did not develop schizophrenia may be attributable to cannabis abuse and/or medication effects.

In fact, in our sample, one patient who transitioned into psychosis was taking antipsychotic medication and 7 who transitioned had never taken an antipsychotic. In comparison, in the UHR group that did not transition, 10 were taking antipsychotic medication and 11 were not. Notably, there was no significant difference in right hippocampal corpus and tail volume between these 4 groups ($F_{3,27} = 0.668$, $p = 0.58$).

Among the UHR patients who transitioned into psychosis, only 1 had previous cannabis abuse (see the 3-month criterion we used[1]), whereas 7 did not use cannabis. Among the UHR patients who did transition, 8 had comorbid cannabis abuse and 13 were free of cannabis abuse. Again, when we compared the volumes of the right hippocampal corpus and tail, we found no significant difference between the groups ($F_{3,27} = 1.146$, $p = 0.35$).

These findings suggest that the differences in the volume of the hippocampus corpus and tail between UHR patients who transitioned into psychosis and those who did not could not be accounted for by the effect of antipsychotic medication or cannabis abuse. Although 2 previous studies did not reveal hippocampal volume differences between converters and nonconverters,[2,3] we believe that it would be premature to rule out anatomic abnormalities in UHR states in these brain regions. Our study indicates that hippocampal volume reduction may precede the onset of schizophrenia and may be present in prodromal stages, independent of medication effects or the presence or absence of cannabis abuse.

Henning Witthaus, MD
Martin Brüne, MD, PhD
Georg Juckel, MD, PhD
Department of Psychiatry
Ruhr University Bochum
LWL University Hospital
Bochum, Germany

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