Cumulative excessive alcohol intoxications lead to neuronal damage and changes in synaptic plasticity. We have examined the expression of cytoskeletal proteins in human post-mortem tissue from the prefrontal cortex. Brain tissue was analysed from 31 alcoholics and 31 age, sex and tissue post-mortem delay matched control subjects. Light microscopy of H&E stained prefrontal cortex tissue revealed a reduction in the levels of cytoskeleton surrounding the nuclei of cortical and subcortical neurons, and a disruption of subcortical neuron patterning in alcoholic subjects. Protein resolution by one dimensional polyacrylamide gel electrophoresis identified significant downregulation of β-spectrin, and α- and β-tubulins. For alcoholic subjects, a significant increase of α-tubulin acetylation, significant increase of protein isoaspartyl methyltransferase levels, and significant reduction of proteasome activity was also observed. Acute alcohol-related brain damage was also modelled in rats administered ethanol for 4 weeks. Brain tissue from ethanol-fed rats also displayed significantly reduced cytoskeletal protein expression. Collectively, these results suggest that damage to the cytoskeletal architecture is a pathological hallmark of alcohol-related brain damage.